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COMMUNICATIONS

EXPERIMENTAL RESEARCH WITH CORNEAL HETEROGRAFTS*

BY

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KERATOPLASTY still poses problems, and the more we extend our experiments to try to elucidate the biology of the tissue fragments incorporated into the cornea, the more the biology appears complex. Until now, it has been almost dogma, because of the failure of most previous attempts, to state that corneal heterografts are not possible; that first they become opaque, and then they are replaced by reactive tissue originating in the receiver. A few workers have succeeded in maintaining fragments of clear transplanted cornea in the cornea of another species, but these experiments have not been very extensive (Bonnefon, 1914; Galante, 1938); and similar work done since has given negative results (Thomas, 1936; Castroviejo, 1937). Though this question seemed to be finally closed, we began further experiments after receiving a personal communication from Dr. Bock, now a collaborator of Professor Maumenee in San Francisco. Bock, while trying to explain the mechanism of opacification of corneal grafts, proposed a technique of implantation which differs from that of perforation and lamellar grafts. The former is followed all too often in the rabbit by infection or inclosure of the iris; with the latter it is difficult to achieve fixation.

Technique

The new method† consists in using a spatula with thin edges to cut the corneal stroma of the receiver starting from a limbal incision, and to slide into the slit so made a rounded edge of the cornea to be grafted. Thus the graft is included between lamellae of the corneal stroma of the recipient, which obviously implies totally different biological conditions from those obtaining with the usual types of graft; *i.e.*, those which are in contact with the surface, and also, in the case of perforating grafts, with the aqueous humour.

This technique, which is simple to perform, has given us in the past 6 months some unexpected results which pose a whole series of new biological problems.

Experiments

We have transplanted into rabbit corneae (by means of Franceschetti's trephine) rounded slivers of cornea (5 mm. in diameter) taken from various species: ox, sheep, horse, pig, guinea-pig, rabbit, and man. The corneae from the first four species, since they were too thick to be introduced as such, were sometimes split, so that some animals received a part of the parenchyma with epithelium, others the posterior part of the stroma

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† Choyce (1949) used a somewhat analogous technique for homografts, and has also used it since then for heterografts. The results of his most recent experiments are described in the adjoining article in this issue of the B.J.O.

with Descemet's membrane and endothelium, and others pieces of full-thickness cornea. The donor-globes were removed at the slaughter-house immediately after the animals' death, put into Ringer's solution (holofusine), and refrigerated for 24 hours. The grafts taken at the moment of transplantation were sometimes slightly opalescent, at others quite transparent. A local antibiotic treatment (aureomycin ointment 3 per cent.) generally served to prevent infection. We watched the evolution of the grafts by repeated slit-lamp control, at first daily for several weeks, and then bi-weekly.

These repeated biomicroscopical controls were supplemented in some cases, by a histological study of the transplants after a period ranging from 8 days to 3½ months. The other animals are still alive.

Results

We operated on 22 rabbits, some bilaterally, and performed a total of 33 grafts. Three grafts were expelled, either exteriorly or into the anterior chamber, but the remaining thirty may be classified into three groups:

(1) Transparent Heterografts.—Some heterogeneous grafts remained clear throughout the period of observation, which ranged from 6 to 3½ months for the most recent (Figs 1 and 2). Their presence in the rabbit cornea produced no inflammatory, oedematous, or vascular reaction. This favourable evolution was observed in twelve eyes which received the following heterografts:

four ox (anterior portion, 3; posterior, 1), two horse (anterior, 1 (Fig. 1); posterior, 1), two pig (total cornea, 1; posterior, 1), one guinea-pig (total cornea, 1), three sheep (total, 1; anterior, 1; posterior, 1). Two rabbit homografts were also successful.

FIG. 1.—Rabbit 121, right eye. Horse interlamellar graft (anterior part of cornea); still clear 6 months after implantation.

FIG. 2.—Rabbit 124, right eye. Human interlamellar graft, 8 days old, no opacification; (reaction from receiver and opacification of graft began in this case after 2 weeks).

This tolerance of a heterogenous tissue does not appear to be a phenomenon peculiar to a given species, nor is it related to the presence of a given portion of the cornea (stroma, anhistic membranes, epithelium), since grafts which come from very different species far removed in the animal series are sometimes tolerated perfectly.

The histological examination of the grafts which remained transparent in the few animals which died between the first week and 3½ months, showed the corneal stroma of the rabbit to be unaffected by the introduction of a foreign body (Figs 3 and 4). Neither inflammatory cellular infiltration, nor vascular neoformation was noted. The fragment of tissue is enclosed between lamellae of normal aspect, though its structure is not altogether normal; *i.e.*, some lamellae are irregular and in places dissociated. This phenomenon is no doubt largely due to the method of implantation and also to the lack of mechanical tension on the tissue. The cells appear rarefied, but, on sections perpendicular to the corneal surface at least, show hardly any pyknosis or other nuclear modifications. The aspect of these corneal fragments can be compared to what is observed when the corneae are kept without fixation for 1 or 2 days at a temperature of 18–20°C. When Descemet's membrane is included in the graft, it frequently folds upon itself, and at times is displaced and partially surrounds the graft. The endothelium is often conserved, at least in part, and does not present any manifest signs of activity. The epithelium, on the other hand, undergoes modifications: in most cases it proliferates and produces important cellular collections in the recipient

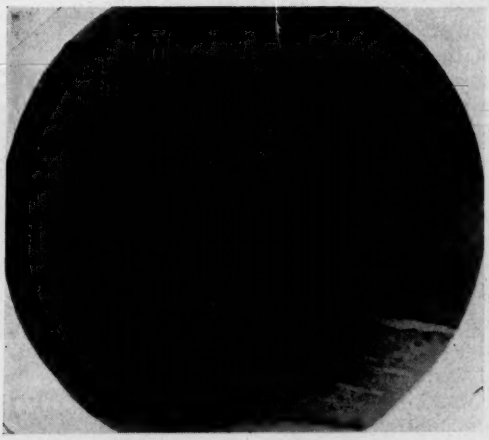

FIG. 3.—Rabbit 140, right eye. Sheep interlamellar graft (full thickness), 12 days old. No reaction in receiver's eye, rabbit's and sheep's epithelia mixed.

FIG. 4.—Rabbit 133, right eye. Ox interlamellar graft (anterior part) 5 weeks old. Enormous epithelial proliferation of graft, no reaction in receiver's eye.

cornea. These are already visible macroscopically and form dull well-defined white spots, which grow slowly and ordinarily provoke no inflammatory or vascular reaction in the host.

Microscopically, these proliferating, heterogeneous, epithelial cells constitute a sort of *in vivo* tissue culture (Fig. 4). When we introduce the heterogenic graft the vitality of its epithelium is still great, a proliferation of the latter in the interlamellar space made by the cleavage is the result. Histological sections of grafts taken between the 18th and 36th day show these epithelial cells to present degenerative changes, atypia, nuclear irregularities, and multinucleated giant cells.

On the other hand, if the cleavage has been done very superficially, small erosions or bullae which burst, and then fill up again, may appear on the surface. In such cases, histological sections show that the graft is well-covered with epithelium, and that it is so embodied within the recipient epithelium that it is impossible to tell which tissue comes from where (Fig. 3).

The vitality of grafted epithelium is a phenomenon already known in the homografts of human cornea we have already described as failures in keratoplasty due to a disordered proliferation of the epithelium of the graft and its host, preventing the normal union of the parenchyma (Babel, 1950; Hervouët, 1952).

(2) Opacified Heterografts.—A certain number of grafts became opaque more or less immediately after their introduction (Fig. 5), and all these produced oedema of the stroma, and pannus-type vascularization in the recipient. These vessels have in common that as a general rule they grow relatively quickly and develop most in that portion of the corneal parenchyma which is anterior to the implant. We have not noted rapid

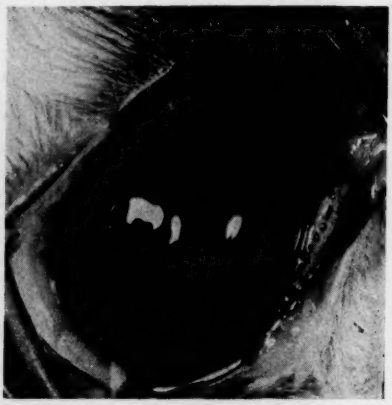

FIG. 5.—Rabbit 139, right eye. Pig interlamellar graft (full thickness), 6 months old, opaque. Note epithelial bubble in inferior region of graft.

FIG. 6.—Rabbit 133, left eye. Pig interlamellar graft (full thickness). Graft into left eye made 2 weeks after graft into right eye (Fig. 4). Important reaction in rabbit cornea from 6th day, no reaction in graft.

vascular invasion into the graft in most of our cases, except in one animal in which there was an infection and resulting necrosis of the graft. Under prolonged observation, the graft is finally seen to be invaded by neoformed vessels.

This reaction on the recipient sometimes starts very early (Rabbit 47: 2 days), but in most cases it begins between the 5th and 12th day. It manifests itself as a small pannus *en epaulette*, but can also be widespread, and progress very quickly. Since this vascularization is accompanied by turbidity of the corneal parenchyma in the recipient, which is partly due to the oedema, and partly to a cellular infiltration (Fig. 6), we treated a series of animals with injections of trypan blue in order to follow the path of the wandering cells. A number of cells in the recipient part of the cornea are coloured blue, but we have not seen this coloration take in the implanted tissue, except in one human corneal graft. In two animals (one with a human corneal graft after 3 days' refrigeration in physiological saline, and the other with a graft of pig cornea after 24 hours) the injection of trypan blue checked the oedematous reaction in the recipient, and brought about an immediate and lasting clearing of the parenchyma, without, however, supressing the infiltrative cellular reaction. The neoformed vessels gradually emptied of their blood, so that after several months they were scarcely visible. Also, even among those animals which did not react with trypan blue to give an immediate clarification, a tardy clearing was seen and the implanted tissue remained transparent for several weeks.

In one case, the reaction was so intense that we thought an abscess had formed, and the animal was killed after 8 days. Histological examination showed that there was no infection but a very violent anaphylactic reaction with a massive eosinophilic infiltration into the tissue of the host and the beginning of an infiltration into the graft (Fig. 7). The sixteen cases of this group may be divided as follows:

one horse cornea (anterior),
four ox cornea (posterior, 2; anterior, 2),
two sheep's cornea (full-thickness),
five pig's cornea (anterior, 1; posterior, 1; full-thickness, 3),
one human cornea,
three grafts of fragments of cornea preserved in formalin (rabbit and pig) or plunged into alcohol for a few minutes (pig).

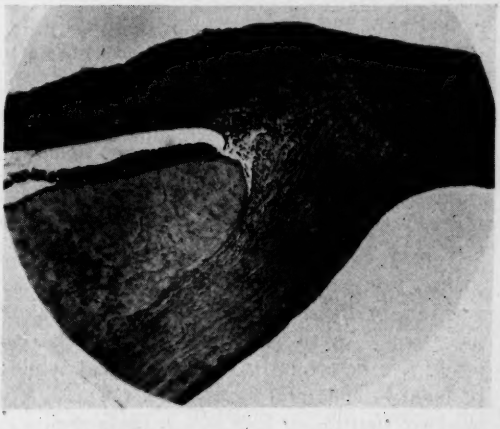

FIG. 7.—Rabbit 47, right eye. Sheep interlamellar graft (full thickness), 8 days old. Massive stroma infiltration of rabbit's cornea by eosinophilic cells, oedema of graft, and epithelial proliferation.

These last experiments, which are to be repeated, showed that in two cases the graft was completely invaded and destroyed by elements from the recipient; and that in the third (rabbit cornea preserved for several weeks in formalin) the cornea, opaque at the moment of the graft, provoked an inflammatory reaction in

the recipient which after several weeks began to clear up steadily, without being invaded by neovascular formations (time of observation: 4 months).

A few workers have already had a partial success with formalinized perforating or lamellar grafts, which can be explained only by the replacement of tissue from the host (Salzer, 1937; Babel, 1950). A few workers have risked implantation of grafts treated with formalin even in man (Scherschewskaya, 1940).

(3) Bilateral Heterografts.—The animals which received grafts to both eyes present interesting data. We treated nine animals in this manner; six had their graft to the second eye 2, 3, or 4 weeks after the first, and all but one received corneae from different species:

ox-pig,	ox-pig,
horse-sheep,	ox-ox,
guinea-pig-sheep,	pig-ox.

With the exception of this last case where the two grafts are still transparent 5 and 4½ months after operation, all the grafts introduced into the second eye became opaque, the reaction beginning between the 5th and 10th day. These cases were similar in evolution and aspect as the single grafts which were badly tolerated. On the other hand, none of the grafts which were clear at the time of the second operation became turbid later (the length of the longest observation was 6 months). One graft was expelled after 14 days.

Histological examination of a few cases shows changes similar to those of grafts which were badly tolerated as a whole: namely, that the reaction is marked in the region of the recipient (infiltration and vascularization) but that the graft takes little part in the process. In a case examined 3½ months after the second intervention, the clear graft was quite free from reactional changes, while in the second eye there was partial invasion by neoformed vessels and cellular elements, lymphocytes, and fibroblasts.

Three other animals received simultaneous bilateral grafts:

horse-horse,
ox-ox,
rabbit (refrigerated 72 hrs)- rabbit (formalin).

Only two grafts remained clear, one in the first and one in the third animal. All the others provoked a strong reaction and became turbid.

Discussion

It may be concluded that interlamellar heterografts into the rabbit's cornea are either well tolerated and remain clear, or induce a defence reaction in the recipient eye. In a total of thirty heterografts, 14 were successful. In twelve animals in which one eye only had been operated upon, five heterografts remained clear while seven were not well tolerated. In eighteen bilateral cases, nine corneae remained clear. As a whole, we may say that about half of our heterografts have been successful. The lack of defence reaction is observed as well in the living animal with the aid of the slit lamp as in histopathological studies. The question whether these transparent heterografts are still living remains to be answered. Histological studies are not much help alone unless special methods are used.*

* The phosphatase reaction, which as a rule can be used as a proof of vitality, is of no value in the corneal tissue, which, except in the epithelium, does not normally contain this enzyme (Süllmann and Payot, 1949; François and Rabaey, 1951).

We have not yet been able to explain the ultimate evolution of these corneal opacifications in the recipient which sometimes clear up and thus differ from the behaviour of the implanted tissues. Indeed, the latter maintains a relative transparency even when its bed becomes opaque.

Evidence is lacking to permit definite conclusions regarding this phenomenon. Corneal opacification is nearly always produced in the second eye, both when we graft pieces of cornea from the same species to both eyes in succession (bilateral graft of ox cornea for example), and when we employ the cornea of different species (ox on one side, for example, and pig on the other). It appears as if in the second eye the heterografts provoked an anaphylactic type of reaction, due not so much to the animal species involved, as to the corneal tissue itself. This point warrants further research. The hypothesis that the existence of tissue groups equivalent to blood groups might explain certain intolerances has already been put forward (Babel, 1950). This should be brought into line with the observations of Maumenee and his school (Müller and Maumenee, 1951a, b) to explain the mechanism of secondary opacification of corneal grafts in the rabbit (homografts) through the influence of an allergic reaction provoked by a subcutaneous implantation of skin from the same donor (experiments which we have been able to confirm personally).

Conclusions

This work, which has only just been begun, and must be followed up by further research before its clinical applications can be considered, has produced the following facts:

(1) a corneal heterograft is feasible, provided a proper technique is utilized, in which the implanted tissues submit to unusual biological conditions (interlamellar graft),

(2) it is possible in this manner to maintain in a transparent state for several months, often without provoking a reaction in the recipient, fragments of corneae coming from different species.

The question of knowing if transplants are alive and remain so, has not been resolved by these initial experiments. The reaction phenomena which they provoke in a certain number of cases appear to be of an allergic type.

Specifically, when bilateral heterografts are performed, the later graft provokes, within the space of a few days, a reaction on the part of the recipient cornea, which at times can be violent and which cannot be explained by an infection but rather by an anaphylactic reaction.

There is a great difference in behaviour between grafted connective tissue stroma which apparently remains passive, and the epithelium which on the contrary proliferates, as it would perhaps in a tissue culture.

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Brit. J. Ophthal. (1952) **36**, 537.

SUCCESSFUL TRANSPLANTATION OF HUMAN AND CAT CORNEAL TISSUE INTO RABBIT CORNEAE*†

BY

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IT is always regarded as axiomatic that there is no possibility of a corneal graft being successful unless the donor material comes from an animal of the same species (Nižetić, 1934; Duke-Elder, 1938; Lister, 1951; Avello, 1951; etc.), but this dogma is open to question.

Ortin (1914, 1916, 1931) performed *penetrating* grafts on rabbits, using donor material from other species; in every case a permanent opacity resulted. He did not state, however, whether the operations had been technically successful and free from complications. For example, adherence of the iris to the graft would by itself have caused opacification of the graft apart from the question of tissue incompatibility between donor and host.

Experimental *lamellar* heteroplasties do not appear to have attracted much attention. Von Walther (cited by Mühlbauer, 1840) made some experiments on animals and operated on a few clinical cases; these efforts were not successful and the report omits histological data and other important details. As no more satisfying reports could be found in the literature it was decided to attempt to fill in this gap in our knowledge.

PRESENT INVESTIGATIONS

Lamellae of corneal tissue superficial to Descemet's membrane were taken from human and cat eyes and grafted into rabbit corneae. It was proposed

(*a*) to kill some animals at lengthening intervals after grafting, in order to study the histological changes taking place,

(*b*) to keep others alive for a minimum period of 2 years, to study the delayed results of these grafts.

TECHNIQUE

The author (Choyce, 1949) described a technique of performing lamellar keratoplasties in rabbits, in which the graft was not held in place by sutures, but was retained by being inserted along the plane of cleavage existing between Descemet's membrane and the deeper layers of the substantia propria. It is rare for the graft to be dislodged after using this technique, and all the experiments to be described in this paper were performed

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† Dedicated to Professor Lindner on the occasion of his 70th birthday.

in this manner. This technique is illustrated by Figs 1 and 2. For full details of the operative technique reference should be made to the original article.

No bilateral heteroplasties were performed.

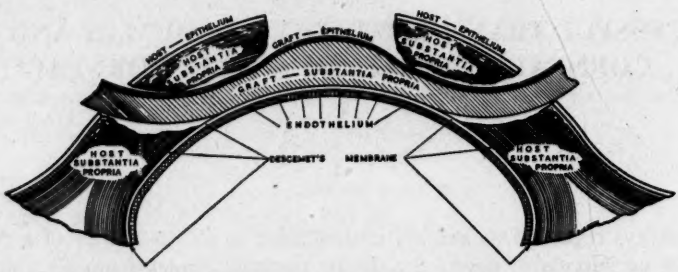

FIG. 1.—Diagram to illustrate intracorneal lamellar keratoplasty (Choyce, 1949).

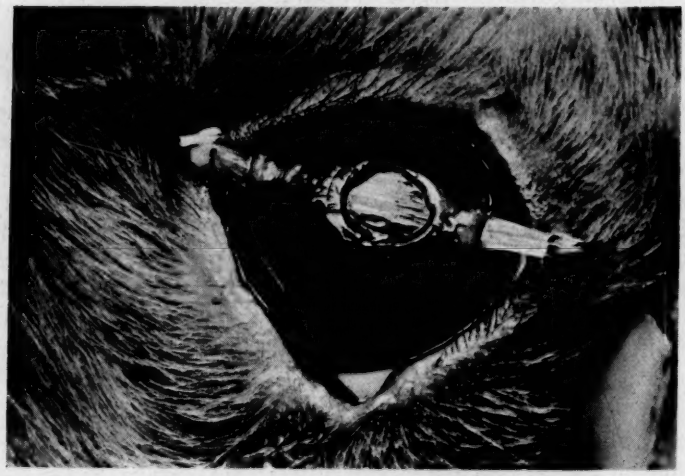

FIG. 2.—Strip of cornea *in situ* (Choyce, 1949).

CLINICAL RESULTS

In any series of survival experiments certain animals die prematurely, *e.g.*, from the effects of the anaesthetic, intercurrent infection, or injuries received from other rabbits in the same cage. These are excluded from consideration. In this particular series a proportion of the animals scratched at their operated eye causing severe ophthalmia. Most of these had to be killed because they were in obvious pain. These also were excluded from analysis of the results.

Some fifteen animals were left for study:

(1) Nine cases of lamellar strip keratoplasty using donor material from cats.
(2) Five cases of lamellar strip keratoplasty using human donor material.

(*a*) IMMEDIATE RESULTS.—The post-operative appearances for both classes of donor material were much the same and bore a striking resemblance to the course of events following homotransplants, as described by the author (Choyce, 1949). The central area of the graft was oedematous; as this subsided translucency returned. There was a variable degree of interstitial keratitis in which superficial and deep vessels invaded the operated area from the two extremities, but in no case was the central area vascularized. After 2 to 3 weeks these vessels disappeared but they could still be detected with the slit-lamp microscope.

(*b*) DELAYED RESULTS.—After 6 or 7 months, the corneae had all healed well. The central areas were translucent and of even surface, as shown by the fact that it was possible to obtain an undistorted view of the rabbits' fundi on direct ophthalmoscopy. Faint markings indicated the sites of operation (Fig. 3).

FIG. 3.—Result of strip lamellar heteroplasty after 7 months. The strip runs from 2 o'clock to 8 o'clock (Choyce, 1949).

After 2 years it was extremely difficult to make out these sites, so well had the grafted tissues been assimilated by the host. The grafts were still perfectly clear and there was nothing to suggest that they would not remain translucent indefinitely. All signs of post-operative keratitis had long since disappeared, there were no ghost vessels, and the operated eyes were almost indistinguishable from their unoperated fellows. In several cases the record made at the time of operation was the only means of deciding which eye to excise for histological examination.

The animals were killed, and the eyes were submitted to histological study. The time which had elapsed since operation varied between 22 and 27 months (average 24 months).

Histological Results

(*a*) Early Findings.—Reference should be made to the adjoining paper by Babel and Bourquin, which includes an account of the histological findings from 8 days to 3½ months after a similar series of operations.

(*b*) Findings Two Years after Grafting.—Vertical sections were made of the corneae along the axes of the operations. In some of the eyes it was very difficult to make out the site of the operation. Figs 4 and 5 show the low-

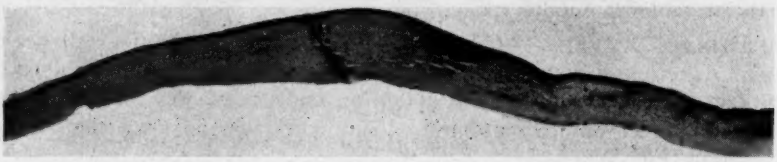

Fig. 4.—Two years after performance of heteroplasty, using human donor material (low-power view).

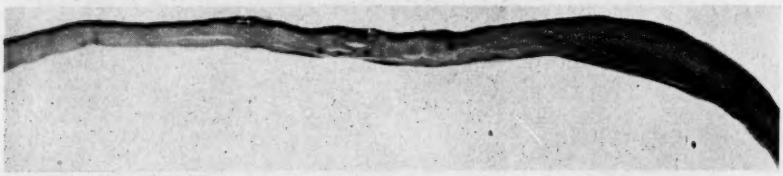

Fig. 5.—Two years after performance of heteroplasty, using donor material from cat (low-power view).

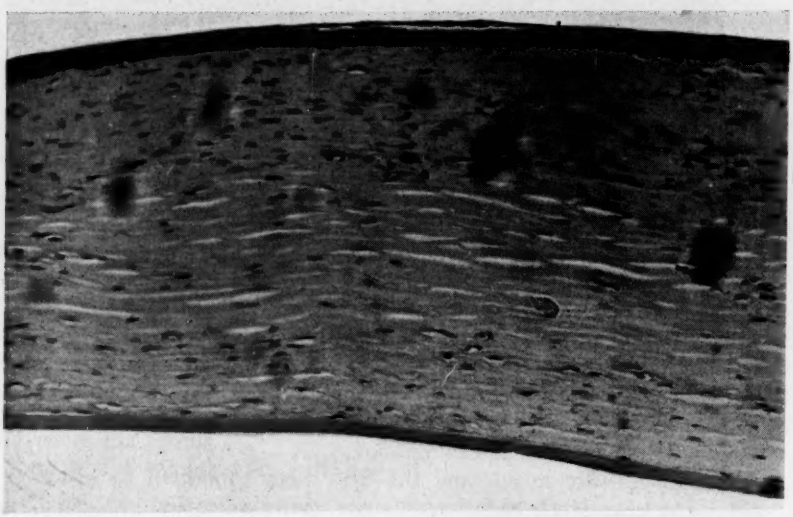

Fig. 6.—Human heteroplasty (high-power view).

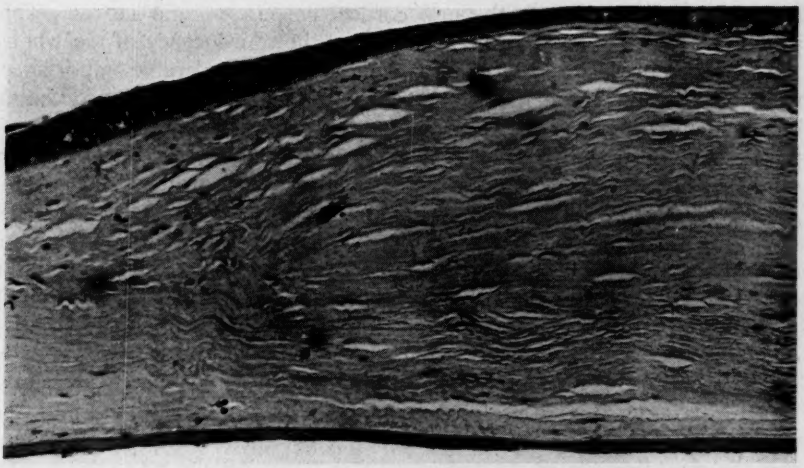

FIG. 7.—Cat heteroplasty (high-power view).

FIG. 8.—Cat heteroplasty, showing irregularity of surface epithelium (high-power view).

power appearances of human and cat heterografts respectively, and Figs 6 and 7 the appearances under high power. It will be noted that there is remarkably little departure from the normal. Slight irregularity of the surface epithelium may be noted at one or two points (Fig. 8) but otherwise little abnormality is seen. There is no trace of the buried foreign epithelium. The dimensions of the corneal corpuscles of man, cat, and rabbit are quite different, and yet the fibres here shown appear to be homogenous and typical of those of the host.

DISCUSSION.—The only possible interpretation of these histological appearances is that, after 24 months, every component of the heterograft has been

replaced by host cells—epithelium, corneal corpuscles, and nerves. This process has been effected without disturbing the translucency of the whole.

The wider implications of these results are of considerable importance, from both scientific and practical aspects. Since two workers, proceeding independently of each other, have shown that experimental *lamellar* heteroplasties are a practical possibility in the rabbit, this may be regarded as an established fact. Logically the next step would be to try to perform *penetrating* heteroplasties in rabbits, and if these were successful the experiments might be repeated further up the zoological scale, *e.g.*, grafting human corneal tissue into Rhesus monkeys. From the scientific stand-point these experiments should illuminate the vexed problem of the " fate of the graft ", while on the practical side there is always the possibility of finding alternative donor material suitable for use in human eyes. The rabbit cornea seems to be very remarkable in many ways, and it would be a mistake to conclude, because it is possible successfully to graft human corneal tissue into the rabbit cornea, that the reverse is also true. Nevertheless, it is acknowledged that the great impediment to graft surgery in Great Britain, up to the present time, has been the lack of suitable donor material. This problem would be grealy simplified if further experiments showed that corneal tissue from other species could be used instead of human donor material.

SUMMARY

(1) Lamellae of corneal tissue from cat and man have been successfully grafted into rabbit corneae.

(2) After 2 years the host corneae were almost indistinguishable from normal, and there was no suggestion that the grafts would not remain translucent indefinitely.

(3) The significance of these observations is discussed.

The costs of this research were met by a grant from the Medical Research Council. My thanks are due to the Pathology Department (Dr. Norman Ashton) and the Medical Illustration Department (Dr. Peter Hansell) of the Institute of Ophthalmology in preparing the sections and the illustrations, and to the Editors of the *Transactions of the Ophthalmological Society of the United Kingdom* for permission to reproduce Figs 1, 2, and 3.

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RADIO-ACTIVE DI-IODOFLUORESCEIN IN THE DIAGNOSIS OF INTRA-OCULAR TUMOURS*†

BY

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London

THE use of radio-active dyes in the localization of brain tumours has been described in recent years by various authors. For example, Boyack and others (1948) found that di-iodofluorescein in which the iodine had been rendered radio-active was preferentially taken up by brain-tumour tissue, so that the position of the tumour could be determined by Geiger-counter measurements made from outside the skull. In a series of 104 cases, Ashkenazy and others (1947) claimed 95 per cent. success in the localization of tumours to one particular quadrant of the brain.

Recently Belcher and Evans (1951) and de Winter (1951) in a very detailed investigation, using the far more sensitive *scintillation counter*, have failed to confirm these results, nor could the selective uptake of the dye in neoplastic tissue be observed in any one of the specimens removed surgically. They concluded that, owing to variations in the vascular character of the brain tissues and radiation from other body organs, even a 20 per cent. change in count-rate due to concentration of activity in a brain tumour, would prove difficult to detect.

In ocular tumours the circumstances are rather different. In the first place, we are dealing with a tissue mass which, although much smaller in volume, is located so superficially that the counter can be applied within 3 cm. of the tumour itself; and in the second place, it is not the localization of the tumour which is sought, that being usually all too apparent ophthalmoscopically, but assistance in the all-important and often perplexing differential diagnosis of such a mass. Although the reason for this concentration in neoplastic tissues and its preference for those of the central nervous system is quite obscure, it seemed likely that both of the important malignant intra-ocular neoplasia, and especially the retinoblastoma, might share this predilection, both being as a rule richly supplied with vessels. At any rate the paramount importance of such a diagnostic test, if it proved successful in determining whether an eye should be removed, seemed to justify this investigation, in spite of discouraging reports by Belcher and Evans, and by de Winter. It should be added that Davis (1951) has already found positive counts in two cases with large malignant melanomata.

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†Dedicated to Professor Lindner on the occasion of his 70th birthday.

Thomas and others (1952) have used another radio-isotope (phosphorus 32) for the same purpose. The β-rays emitted by phosphorus 32 have a maximum range in tissue of about 7 mm., which means that a concentration of the isotope lying at a depth greater than this would go undetected. The authors point out that by using this isotope the effects of the active material lying at a greater depth or circulating in the blood are thereby obviated and this should result in a clearer picture being obtained. The disadvantage of this method lies in the fact that lesions in the posterior part of the eye were only made reasonably accessible to observation by rotation and fixation of the eye. These disadvantages are obviated by the use of di-iodofluorescein incorporating radio-active iodine 131 and emitting γ rays which can be detected after they have passed through several centimetres of tissue.

Technique

To avoid radiation hazard it was thought advisable to use an amount of dye containing not more than 1 mc. radio-iodine for each patient. The dye, in approximately 2 ml. solution, was injected intravenously, and, following the practice of other workers, counting* was begun from 2 to 4 hours after injection. The counter tube (type G.M. 4) was shielded laterally by 1 cm. lead to absorb radiation from other parts of the body as far as possible. The aperture of this lead shield was 2.5 cm.

TABLE

ANALYSIS OF CASES TESTED (1–9 Malignant

Case No.	Sex	Age (yrs)	Clinical Details							Amount Injected (mc.)
			Side	Site	Extension	Size	Reticulin	Blood sinuses	Pigment	
1	F	32	L	Macula	Sclera	++	+	++	+	0·74
2	F	82	R	Equator	Ciliary body and anterior chamber	++	+	++	++	0·37
3	F	51	R	Macula	Sclera	+	++	++	+	1·0
4	F	50	R	Limbus	Sclera	—	—	—	++	0·8
5	F	68	R	Iris	Ciliary body	+	—	—	—	1
6	F	60	L	Equator	Presumed non-malignant	—	—	—	—	1
7	M	60	L	Disk	—	++	++	++	+++	1
8	M	65	R	Quadrant	Sclera	++	++	++	++	0·8
9	F	61	L	Lower equator	—	—	—	—	—	1
10	F	6 mths	L	Nasal equator	—	—	—	—	—	0·1
11	M	10 wks	R	Retrolental	Presumed non-malignant	—	—	—	—	0·1

* The count-rate meter is made by Panax Equipment, Ltd.

In all cases the count rates were quite low, in some cases so low as to be almost beyond the range of the instrument; and the authors feel that too much reliance should not be placed on any asymmetry between the count rates over each eye, quite apart from the possible physiological significance of such differences. Unfortunately a scintillation counter was not available at the time when these experiments were performed.

Clinical Results

Eight cases of malignant melanomata, and one of retinoblastoma were investigated. One further case of each (Cases 6 and 11) was also tested, but the diagnosis was too uncertain to justify removal of the eye, and the subsequent absence of growth of the tumour in each case has confirmed their non-malignant nature; they are, however, included in the Table below, since their findings have some relevance as controls.

Malignant Melanomata.—These varied in size from a small limbal nodule (Case 4) to which the counter could be directly applied, to several that had extended well into the vitreous cavity, and one (Case 2) that had invaded the anterior chamber.

Case 4 was of especial interest in that there was no increase in the counting rate over the tumour as compared with the corresponding point on the other

Melanoma; 10 and 11 Retinoblastoma)

Count Rates (min.)								Thyroid Count	Thigh Count	Remarks
Over to eye		Below to eye		Above to eye		Lateral to eye				
L	R	L	R	L	R	L	R			
260 30	200 60			180 40	180 90	200	250	600	250	No significant difference Slight increase on right Count rate very low
180	180	180	200	150	140	150	150	500	300	No significant difference
900 700	900 700	700	700	800	800	600 750	1050 750	1600	1200	See note below No significant difference
600	600					600	600	1000	300	No significant difference
500	500	500	500	450	450	450	550	550	250	No significant difference
200	200	150	150	140	150	120	150	350	150	No significant difference
450	500	800	850	450	550	450	650	1000	800	No significant difference
600	550	650	850	500	600	600	700	900	650	Higher counts on right Right eye enucleated
2900	2700–2900	—	—	—	—	—	—	—	—	No significant difference Other readings not possible

eye, but over an area between the right auditory meatus and the right outer canthus the count rate was some 50 per cent. greater than over the left side.

In only one of this small series of eleven cases (Case 2) was there a significant asymmetry in the counts, and unfortunately these readings were near the limits of sensitivity of the instrument. In one other case (Case 4) the increased uptake was observed not over the tumour itself but posterior to it, and in another (Case 9) slightly higher readings were found over the unaffected eye.

It is interesting to note that the count rate over the thyroid gland did not greatly exceed that over the thigh, which shows that the iodine incorporated in the dye is not in a form which is readily taken up by the gland. This seems to indicate that the test should involve little radiation hazard to the thyroid, because of selective iodine concentration.

Retinoblastoma.—This single case can give little indication as to the possible use of radio-active testing as a diagnostic measure, but the practical difficulties of intravenous injection and exact application of the counter to a small and struggling infant hardly encourage the use of this method if further results are as negative as that recorded here.

As a final discouragement against its routine use in diagnosis it may be added that there is an inevitable difficulty in obtaining adequate doses of the radio-active drug to coincide with the discovery of such rare intra-ocular tumours, since neither can wait for the other—the di-iodofluorescein losing its potency, and the tumour progressing.

Summary

The selective uptake of the radio-active dye by the melanoma is very small or negligible as compared with that in the rest of the body, and the authors do not feel that this technique can be recommended as a routine diagnostic procedure.

Our acknowledgements are due to the surgeons of the Moorfields, Westminster and Central Eye Hospital for permission to examine their patients, to Dr. Norman Ashton, Director of Pathology at the Institute of Ophthalmology, for the pathological reports, and to Sir Stanford Cade, who is in charge of the Isotope Unit at the Westminster Hospital, for permission to undertake this investigation.

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CHOROIDEREMIA*

CLINICAL AND GENETIC ASPECTS

BY

ARNOLD SORSBY, A. FRANCESCHETTI, RUBY JOSEPH, AND J. B. DAVEY

Review of Literature

(1) HISTORICAL.—In the fully-developed state, choroideremia presents a characteristic and unmistakable picture of which Fig. 1 and Colour Plate 1(*a* and *b*) may be taken as examples. The almost total lack of choroidal vessels strongly suggests a developmental anomaly. In fact most of the early writers on the subject, such as Mauthner (1872) and Koenig (1874), stressed the likeness to choroidal coloboma. As cases accumulated, less extreme pictures were observed, and these raised the possibility that choroideremia was a progressive affection and not a congenital anomaly—a view that gained some support from the fact that, apart from showing some choroidal vessels, these less extreme cases also showed pigmentary changes, sometimes reminiscent of retinitis pigmentosa (Zorn, 1920; Beckershaus, 1926; Werkle, 1931). Furthermore, the recognition of gyrate atrophy as a separate entity (Cutler, 1895) fitted in well with such a reading. The patches of atrophy seen in that affection could well be visualized as an early stage of the generalized atrophy seen in choroideremia, and since there was some evidence that gyrate atrophy was itself a variant of retinitis pigmentosa—for the affection is reputed to have been observed in families diagnosed as suffering from retinitis pigmentosa (*see* Usher, 1935)—the suggestion emerged that choroideremia, far from being a congenital stationary affection, was an extreme variant of retinitis pigmentosa. The occurrence of nightblindness as a cardinal symptom in all three affections appeared to lend additional support to the idea of their unity—a view still further supported by the fact that retinitis pigmentosa had been recorded in families with choroideremia by Smith and Usher (1916) and by Beckershaus (1926).

Three possible readings of choroideremia therefore emerged. At the one extreme it was regarded as an independent, congenital, stationary affection; in sharp contrast to this view it was regarded as an extreme variant of retinitis pigmentosa with its abiotrophic character; thirdly it figured as an independent affection, possibly congenital, but undoubtedly progressive. These difficulties, which could not be resolved by the case reports, have been cleared up in recent years by genetic studies. It is now established that choroideremia is an independent affection unrelated to retinitis pigmentosa. Whether the

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affection is congenital is still not known, though there is no doubt that it is progressive. It is likewise certain that choroideremia is unrelated to gyrate atrophy, whatever doubts may still exist regarding the status of gyrate atrophy as an affection independent of retinitis pigmentosa—or indeed as a genuine clinical entity.

(2) CASE REPORTS WITHOUT CRITICAL GENETIC STUDIES.—Between 1872, when Mauthner recorded the first case of choroideremia, and the year 1948, some fifty cases have been reported in the literature (Table I). These are all fairly convincing examples of the affection, though not all were originally recorded as choroideremia. Six essential points emerge:

(*i*) Excepting the cases recorded by Grimsdale (1917) and by Shapira and Sitney (1943), all the patients were men.

(*ii*) In twelve instances, one or more brothers were affected (Mauthner, 1872; Koenig, 1874; Bullar, 1898; Alexander, 1910; Wolf, 1930; Bedell, 1937; Bencini, 1938; Sorsby, 1939; Scobee, 1943; Saebø, 1948).

(*iii*) A maternal grandfather was recorded by Würdemann (1935) as having had a similar condition, and Zorn (1920) and Schutzbach (1938) noted the affection in a man and in his sister's son respectively.

(*iv*) In one instance, a maternal uncle had "typical retinitis pigmentosa" [not further specified] (Beckershaus, 1926); in another, a maternal uncle had "bad sight" (Alexander, 1910); two uncles [relationship unspecified] were reported to have poor vision (Esterman, 1947); "similar trouble" was noted in a grand-uncle (Thompson, 1899).

(*v*) "Typical" or "atypical" retinitis pigmentosa, or other indefinite fundus lesions, were observed in some of the women in the families of patients with choroideremia by Smith and Usher (1916), Zorn (1920), Beckershaus (1926), Schutzbach (1938), Bencini (1938), Sorsby (1939), and Saebø (1948).

(*vi*) Progressive increase in the ophthalmoscopic changes were observed in five cases:

(1) Thompson (1899) and Wardale (1906),
(2) Smith and Usher (1916) and Riddell (1939),
(3) Connor (1919) and Bedell (1937),
(4) De Schweinitz's case in Parker and Fralick (1931) and Bedell (1937),
(5) Zorn (1920) and Schutzbach (1938).

One case was recorded as having been stationary for 6 years (Cowgill, 1892).

(3) CRITICAL GENETIC STUDIES.—Goedbloed (1942) and Waardenburg (1942) independently drew attention to the possibility that choroideremia is an intermediate sex-linked affection. Goedbloed based his observation on an affected man whose sister and mother showed a fundus anomaly of the pepper and salt type without visual symptoms, and he found support for his reading in a brief survey of previously reported cases. Waardenburg's conclusion was based on a detailed analysis of the literature. In particular, the follow-up study by Schutzbach (1938) of the cases originally reported by

TABLE I

CASES OF CHOROIDEREMIA RECORDED BETWEEN 1872 AND 1948

Author and Date	Sex	Age at Examination	Duration of Symptoms	Family History	Remarks
Mauthner (1872)	M	32	Poor vision as long as he could remember, worse at night	Family of nine children, seven sisters well, one brother said to have same type of visual defect	
Koenig (1874) ...	M	20	Poor vision as long as he could remember, nightblind	Brother similarly affected, parents and grandparents said to have normal vision	
	M	Younger brother of above—age not given	—ditto—	Brother of above	
Cowgill (1892) ...	M	17	Poor vision all his life	Not given	Followed for 6 years, no worse
Bullar (1898) ...	M	16	Poor vision all his life	Family of seven children, two brothers said to have bad sight, no consanguinity	
Thompson (1901) and Wardale (1906)	M	18 in 1899	Since early infancy	No consanguinity, parents had good vision, a grand-uncle said to have similar trouble	When seen by Wardale in 1906, condition of fundus stationary but vision declined later
Landmann (1906)	M	44	Vision had always been poor	Father myopic, no further family history	
Marbaix (1908)	M	40	Nightblind as long as he could remember	Not given	
Alexander (1910)	M	31	Had always been nightblind	One of a family of eleven children, nine siblings healthy, one older brother similarly affected, mother had a brother and cousin (? sex) with bad sight —particularly in dim light, no consanguinity	
Smith and Usher (1916)	M	24	Nightblind since childhood	One of a sibship of four, mother and one sister said to have atypical retinitis pigmentosa, father had congenital stationary blindness	
Grimsdale (1917)	F	23	No history available	Not recorded	Family history unobtainable retrospectively (Bridgeman)
Connor (1919) ...	M	25	Nightblind as long as he could remember	Parents not consanguineous, sister and brother well, maternal uncle had repeated attacks of sore eyes	Fundi remained the same 16 years later, but fields were more contracted
Zorn (1920) ...	M	29	Helpless in the dark, nightblind since childhood	One of a sibship of three, mother, one sister and her son, one of his three daughters and one son of the normal sister were nightblind	
Beckershaus (1926)	M	33	Nightblindness noticed in school	No consanguinity recorded, two first cousins and maternal uncle with typical retinitis pigmentosa	
Dimmer and Pillat (1927)	M	44	—	—	No other details beyond a typical illustration
Wolf (1930) ...	M	42	Poor vision since childhood	One of a sibship of five, three brothers normal, one brother similarly affected, father had good vision, mother said to have poor vision—cause not known	
	M	40	—ditto —	Younger brother of above	
de Schweinitz (1931)	M	14	Always had poor vision	No consanguinity; parents both healthy	Constant lateral nystagmus and lens opacities

—continued overleaf

TABLE I—*continued*

Author and Date	Sex	Age at Examination	Duration of Symptoms	Family History	Remarks
Parker and Fralick (1931)	M	33	Nightblind as long as he could remember, always near-sighted	Parents not consanguineous, two sisters said to be normal	
Werkle (1931) ...	M	10	Nightblind	Mother, her sister's son, and his daughter, affected by nightblindness and milder fundus changes	Recorded as gyrate atrophy, but these cases are almost certainly early stages of choroideremia
	M	20	—ditto—	Brother of above	
	M	50	Nightblind since childhood	No consanguinity recorded, has a blind sister—cause not known	
Bahn (1932) ...	M	42	Nightblind		No further details
Wilmer (1934)	M	65	Nightblind	Not given	Photographic exhibit, atlas plate; after 8 years, lens opacities not increased, but slight increase of atrophy of choroid
Bhaduri (1934)	M	17	Sight noted defective at the age of 3 years	One brother myopic	
Würdemann (1935)	M	40	Practically blind since childhood		
	M	35	Always near-sighted	Grandfather (maternal) has similar condition	
Benedict (1937)	M	48	Nightblind since age 6, and near-sighted since age 12	Parents second cousins, one brother wore glasses but had good vision	
Bedell (1937) ...	M	59	Always nightblind	"One brother had similar condition"	
	M	45	Nightblind since childhood	Brother similarly affected, parents, four sisters, and one brother normal	
	M	57	Vision poor for 29 years	Two brothers similarly affected, own two children normal	
	M	43	Steadily increasing nightblindness	Brother of above	
	M	34	Nightblind for 10 years	Third brother of above	
Schutzbach (1938)	M	27	Nightblind, good central vision	Maternal uncle likewise affected	Member of family recorded by Zorn (1920)
Bencini (1938) ...	M	35	Progressive nightblindness	Three sisters and her children normal	Progressive deterioration in both patients over 3 years
	M	38	—	Brother of above, ?pathological fundus in mother and in the son of elder brother	
Sorsby (1939) ...	M	43	Progressive nightblindness	Two brothers, parents not consanguineous	Recorded as cases of choroidal sclerosis, more fully studied in this paper
	M	54	—ditto—	A sister shows lesions suggestive of old "central choroiditis"	
(1940)	M	28	Progressive symptoms	Wrongly recorded as clear	More fully studied in this paper
Goedbloed (1942)	M	38	Progressive symptoms	Mother and sister show pepper and salt fundus	
Shapira and Sitney (1943)	F	52	Poor vision since childhood	Not given	Hypertensive disease, Wassermann reaction ++, family history not obtainable retrospectively (Shapira, 1951)
Scobee (1943) ...	M	24	Nightblindness recently		Mother shows mild arteriosclerotic retinopathy
	M	18	No subjective symptoms, examined because of findings in brother	Brother of above; another brother and two sisters normal	

—*continued opposite*

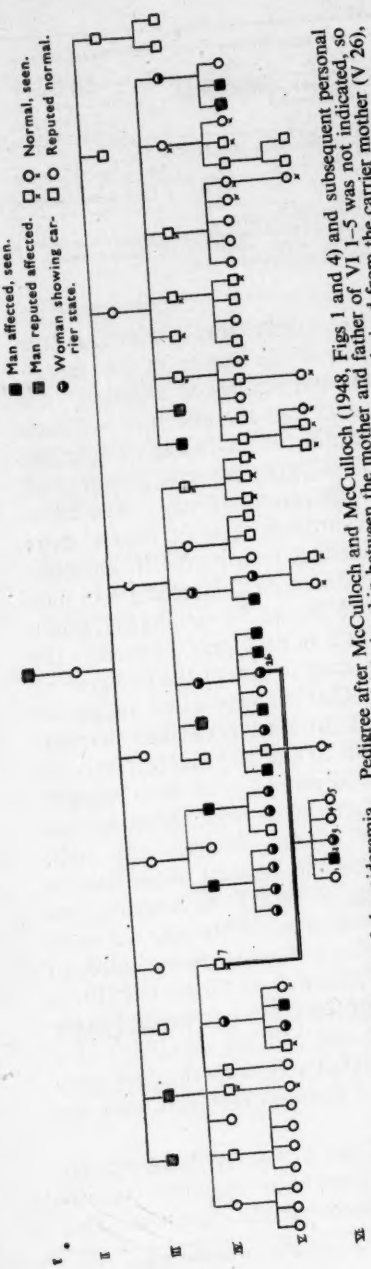
TABLE I—*continued*

Author and Date	Sex	Age at Examination	Duration of Symptoms	Family History	Remarks
Magder (1945)	M	58	Progressively night-blind since child-hood	Isolated case in large sibship, parents normal	
Ésterman (1947)	M	29	Nightblind	Two uncles said to have poor vision	
Meyran (1948)	M	7			Case seen in abstract
Saebö (1948) ...	M	27	Nightblind since childhood	Four affected brothers	Reported as cases of gyrate atrophy
	M	38	Nightblind at 20	Two brothers and three sisters normal, mother shows in-definite changes around disks	
	M	44	Nightblind in youth		
	M	46	Blind at 40		

Zorn (1920) strongly suggested that possibility. Schutzbach, who like Zorn had noted an unusual fundus reaction in some of the women in that family, concluded that choroideremia is a dominant and sex-linked affection. He based his assumption of dominance on the fact that the affection had been transmitted over three generations, and his reading of sex-linkage on the fact that only the men were markedly affected—an unnecessarily complicated reading which is in any case inconsistent with genetic theory. The interpretation given by both Goedbloed and Waardenburg is of course more satisfying. The assumption that choroideremia is transmitted in an intermediate sex-linked manner implies that it produces the full affection in men (as they possess only one X-chromosome which carries the pathogenic gene), and an abortive form in women (as they have a normal gene to modify the pathogenic gene). Though Waardenburg appears to accept the pedigree by Werkle (1931) as illustrative of gyrate atrophy, that pedigree is also suggestive of the inheritance of choroideremia in an intermediate sex-linked manner. The illustrations given for the two brothers aged 20 and 10 years respectively, and the nightblindness and indefinite fundus appearances in their mother, and in her sister's son and daughter, all conform better with choroideremia than with gyrate atrophy. Waardenburg's careful analysis left some difficulties unanswered, the chief of which was the reputed occurrence of four cases in women.* He excluded only that of Werkle as doubtful, but actually the cases of Hutchinson (1900) and Thompson (1899)—the record of the latter he could not obtain in the original—should likewise be excluded, so that only one authentic case in a woman—that recorded by Grimsdale (1917)—is left for consideration. Whatever doubts may have remained were dissipated by the model study of McCulloch and McCulloch (1948) of a family with over 600 members, including 33 affected and 53 carriers—a study further supported by that of a second family of eighteen members with five affected and five carriers.

These extensive pedigrees (of which Pedigree Chart 1, overleaf, is an extract) further cleared up the confusion in the early literature as to ' atypical ' retinitis pigmentosa occurring in the women of choroideremia families. This

* The case subsequently reported by Shapira and Sitney (1943) would have raised the number to five.



PEDIGREE CHART 1.—Inheritance of choroideremia. Pedigree after McCulloch and McCulloch (1948, Figs 1 and 4) and subsequent personal communications. In the pedigree as originally published, the relationship between the mother and father of VI 1–5 was not indicated, so that it appeared that an unaffected man (IV, 7) had affected children, whereas in fact their affection derived from the carrier mother (V 26), who was the father's second cousin. We are indebted to Dr. R. J. P. McCulloch for the additional information shown here.

difficulty is adequately resolved by the conception of the carrier state as an essentially symptomless disorder producing somewhat variable ophthalmoscopic changes.

The earliest ages at which the affection was observed in boys by the McCullochs were 6 and 7 years—and possibly also 22 months—which makes it likely that choroideremia is a congenital and not an abiotrophic defect. Their material also confirmed the earlier findings that the affection is progressive.

One further pedigree has since been published (Lowe, 1951). This shows the affection in a man, transmitted through a carrier daughter to one of her three sons (Pedigree Chart 2, opposite).

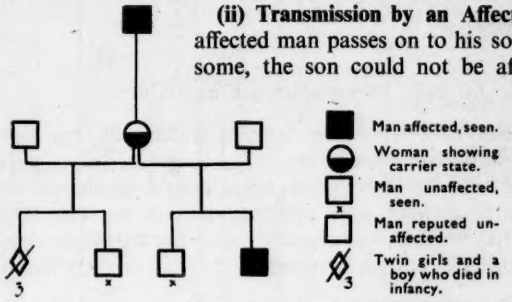
(4) SOME OUTSTANDING DIFFICULTIES

(i) Transmission by Unaffected Men.—No unaffected man should pass on an intermediate sex-linked disorder. This expectation does not appear to have been realized in two families:

(*a*) *Schutzbach's Pedigree.*—This pedigree shows an affected son of a normal father, whose brother showed typical choroideremia. On Schutzbach's own findings this case must be regarded as most doubtful.

(*b*) *The McCullochs' Pedigrees.*—These contain two deviations from expectation. In one case a normal man has a carrier daughter (McCulloch, Fig. 2); in another case a normal man has a carrier daughter and an affected son (*ibid.*, Fig. 4). Actually, as Dr. R. J. P. McCulloch informs us, the affected individuals were the offspring of carrier women. The carrier daughter of a normal man shown in McCuloch's Fig. 2 was the offspring of a marriage of cousins—III, 4 having married III, 31, a woman

who was a known carrier. Likewise the affected son, V, 3 and his carrier sister, V, 4 (McCulloch, Fig. 4) were the offspring of a marriage between an observed carrier IV, 31 and her cousin once removed, III, 7. The amended data in this second case are shown in Pedigree Chart 1, where the parents in question appear as IV, 7, and V, 26.



PEDIGREE CHART 2.—Inheritance of choroideremia (after Lowe, 1951).

(ii) Transmission by an Affected Man to his Son.—As an affected man passes on to his son only his normal Y-chromosome, the son could not be affected. Apparent exceptions are recorded by di Marzio (1937) and by Bencini (1938).

In di Marzio's case, illustrated and briefly described in his Atlas as a case of "total congenital sclerosis of the choroidal vessels (choroideremia)", a man is recorded as having a brother and a son affected with "atypical retinitis pigmentosa". But the diagnosis of choroideremia seems unwarranted; the illustration shows a pigmented central area with sclerosed choroidal vessels rather than the characteristically retained normal central area, and the disk and vessels are of the retinitis pigmentosa type.

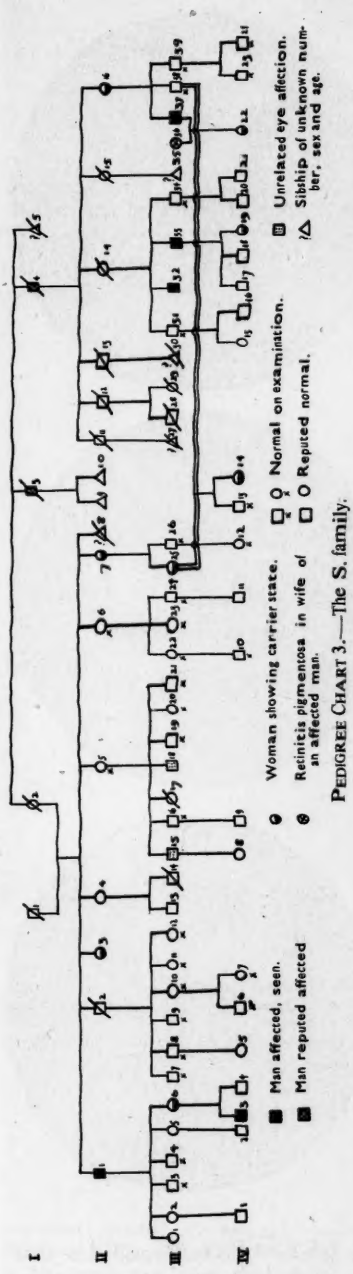
In Bencini's case an affected man is reported as having an affected son, but as the son showed indefinite peripheral fundus changes without functional disturbances the findings are hardly conclusive.

(iii) Occurrence in Women.—Since the publication by Grimsdale (1917) of a case of choroideremia in a woman, there is another case report to consider (Shapira and Sitney, 1943). Theoretically a woman can show choroideremia only if her father was affected and married a carrier. Unfortunately, neither case report gives a family history, and attempts to obtain them retrospectively proved unsuccessful (Bridgeman, 1951; Shapira, 1951). A case, reported by Thompson (1899) as "superficial choroidal atrophy without subjective symptoms, in a member of a family subject to nightblindness", is a good example of the carrier state, and not of choroideremia. The case of Hutchinson (1900) is one of choroidal sclerosis included in the original cases of the Laurence-Biedl syndrome (Laurence and Moon, 1866); it is recorded by Hutchinson as a case not of choroideremia, but of "disease of the choroids".

(iv) Relationship to Retinitis Pigmentosa.—If choroideremia is an entity distinct from retinitis pigmentosa, this latter should not occur as a variant of choroideremia in a choroideremia family. Two of the older pedigrees do not appear to conform:

(*a*) *Smith-Usher Pedigree.*—Here the sister of a markedly affected man showed 'atypical' retinitis pigmentosa, while the mother was recorded as showing retinitis pigmentosa. It is not unlikely that the mother merely showed a more severe form of the carrier state than the daughter (Usher, 1935; Riddell, 1939; 1950).

(*b*) *Beckershaus* (*1926*).—The occurrence of retinitis pigmentosa in the maternal uncle of a man with choroideremia and in this uncle's son and daughter is reported without any further detail. This account is too scanty to allow a critical judgment.



PEDIGREE CHART 3.—The S. family.

(S II, 1) is an affected man, and the remaining five are women, two of whom are normal while three (S II, 3, 7, and 16) show variable ophthalmoscopic appearances without any subjective symptoms.

In the third generation three affected men (S III, 32, 33, and 37) were observed, and there were also two women (S III, 6 and 25) with symptomless ophthalmoscopic changes.

In the fourth generation there is an affected boy (S IV, 3) and three girls with ophthalmoscopic anomalies (S IV, 14, 19, and 22).

Taking the family as a whole there are therefore five affected men and eight women with symptomless ophthalmoscopic lesions. The personal details are shown in the Appendix and are summarized in the legends to the relevant illustrations.

Ophthalmoscopic Appearances and Subjective Symptoms in the Men.—The five affected males (S II, 1; S III, 32, 33, and 37; S IV, 3) were aged 69, 56, 55, 41, and 6½ respectively. The range of fundus appearances in the patients aged 69, 56, 41, and 6½ is shown in Fig. 1 and Colour Plate 1(*a*), (*b*), and (*f*); fundus drawings of S III, 33, a man aged 55, could not be obtained, but the appearances were almost identical with those of his brother (S III, 32) seen in Colour Plate 1(*a*). The outstanding subjective features in the four adult cases were consciousness of nightblindness in the early years of life and increasing constriction of the visual fields. The progressive character of the affection was noted ophthalmoscopically in one case (S III, 37). He was first seen in 1937 when he was 28 years old and already certifiably blind. The fundus at that time is shown in Colour Plate 1(*c*) which, in contrast with Colour Plate 1(*b*) taken in 1950, still shows some choroidal vessels. In this man serious visual defect, which compelled him to give up his work as a tailor, had become established by the age of 18.

[Two brothers in the S family (S III, 15 and 18) show bilateral central fundus lesions with evident choroidal sclerosis and patches of choroidal atrophy and pigmentation. Their mother is normal and there is nothing to suggest choroideremia in the sons, the elder of whom also shows lens changes.]

Ophthalmoscopic Appearances in the Women.—The ages of the eight unaffected females showing ophthalmoscopic lesions (S II, 3, 7, and 16; S III, 6 and 25; S IV, 14, 19, and 22) ranged from 6

(5) A POSSIBLE CONGENITAL TYPE.—The existence of choroideremia as a progressive affection seen early in childhood suggests that the affection is congenital in origin, but does not exclude the possibility which emerges from the older literature that there is a congenital stationary type. For the present this remains hypothetical.

(6) MORBID HISTOLOGY.—So far only two studies are available:

(*i*) *McCulloch* (*1950*).—Four eyes from the families studied by the two McCullochs (1948) came to histological examination. The choroidal vessels were either sclerosed or absent, and the outer layers of the retina extensively degenerate or totally lacking. The retinal changes were proportionate to the choroidal changes throughout; where the choroid was relatively intact the retina appeared to be least involved. The choroidal changes were regarded as the primary lesion.

(*ii*) *Fornes Peris* (*1947*).—This is a doubtful report based exclusively on *post-mortem* findings. A girl aged 3 was found to show complete absence of the choroid. In the absence of a clinical report, and in view of the sex and age of the patient, the exact status of the finding must be regarded as uncertain.

(7) CLINICAL APPEARANCES.—There is room for a clearer appreciation of the range of changes, and rate of progress of the affection as seen in men, and of the anomalies as seen in women. The present study was undertaken largely with this object in view.

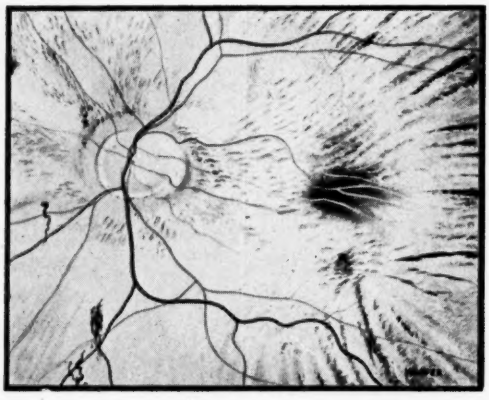


FIG. 1.—Left fundus of S II, 1, male, aged 69. Note almost total atrophy of retina and choroid, including atrophy in central areas where some pigmentation persists. Nightblindness has been present since early childhood, and the patient has been blind since the age of about 55, his vision being perception of light only.

Material of Present Investigations*

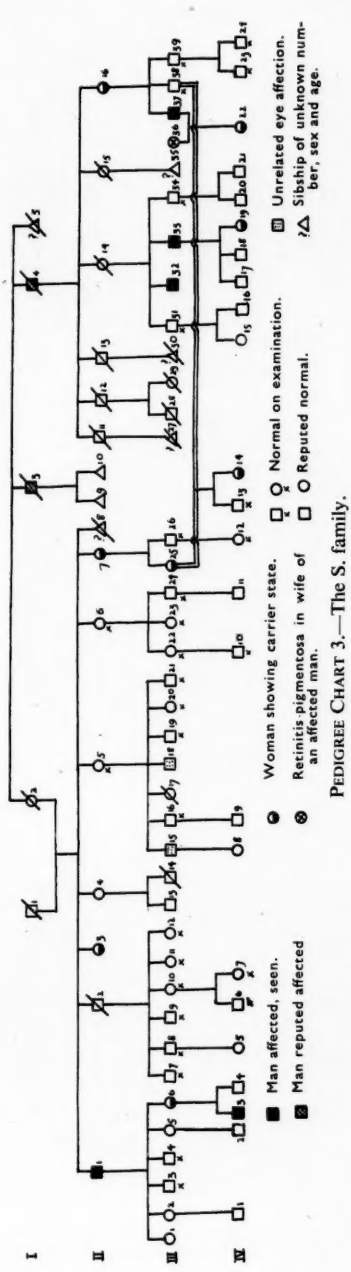
Three families, one fairly large, and the other two rather small, were investigated. One member of each of the first two families had previously been recorded as an isolated case of an unusual form of choroideremia (Sorsby, 1939, 1940).

(1) The S. Family (Pedigree Chart 3, opposite)

The members of the first generation are all dead. Two men in this generation are reputed to have been affected.

In the second generation seven members are alive and six could be examined. Of these six, one

* The contribution of one of us (A. F.) was limited to the study of the descendants of S II, 14.



PEDIGREE CHART 3.—The S. family.

(S II, 1) is an affected man, and the remaining five are women, two of whom are normal while three (S II, 3, 7, and 16) show variable ophthalmoscopic appearances without any subjective symptoms.

In the third generation three affected men (S III, 32, 33, and 37) were observed, and there were also two women (S III, 6 and 25) with symptomless ophthalmoscopic changes.

In the fourth generation there is an affected boy (S IV, 3) and three girls with ophthalmoscopic anomalies (S IV, 14, 19, and 22).

Taking the family as a whole there are therefore five affected men and eight women with symptomless ophthalmoscopic lesions. The personal details are shown in the Appendix and are summarized in the legends to the relevant illustrations.

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[Two brothers in the S family (S III, 15 and 18) show bilateral central fundus lesions with evident choroidal sclerosis and patches of choroidal atrophy and pigmentation. Their mother is normal and there is nothing to suggest choroideremia in the sons, the elder of whom also shows lens changes.]

Ophthalmoscopic Appearances in the Women.—The ages of the eight unaffected females showing ophthalmoscopic lesions (S II, 3, 7, and 16; S III, 6 and 25; S IV, 14, 19, and 22) ranged from 6

FIG. 2.—Left fundus of S II, 3, female, aged 65, sister of an affected man, S II, 1 (Fig. 1). No children.

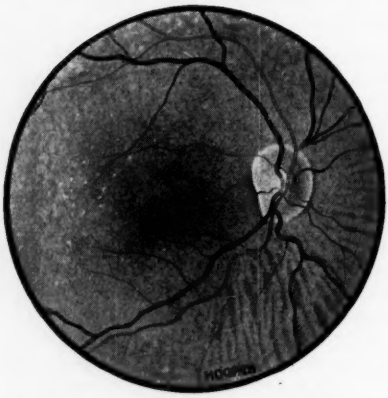


FIG. 3.—Right fundus of S II, 7, female, aged 55, sister of an affected man, S II, 1 (Fig. 1) and mother of a carrier daughter, S III, 25 (Fig. 4), and a carrier granddaughter, S IV, 14 (Fig. 6). The anomalies are not very marked.

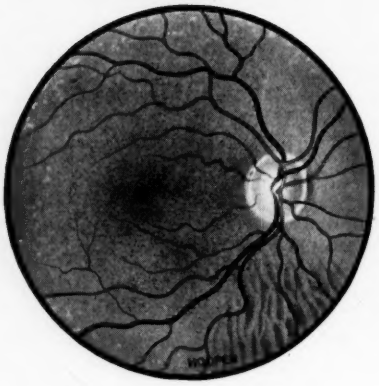


FIG. 4.—Right fundus of S III, 25, female, aged 31, daughter of S II, 7, a carrier (Fig. 3), and mother of S IV, 14, also a carrier (Fig. 6). Note the similarity to the mother's fundus (Fig. 3).

to 65 years. Fig. 2, Colour Plate 2(*b*), Figs 3, 4, 5, Colour Plate 2(*a*), and Figs 6 and 7 give the appearances in chronological order. Subjectively none was conscious of

FIG. 5.—Left fundus of S III, 6, female, aged 27, daughter of an affected man, S II, 1 (Fig. 1), and mother of an affected son, S IV, 3 (Colour Plate 1*f*).

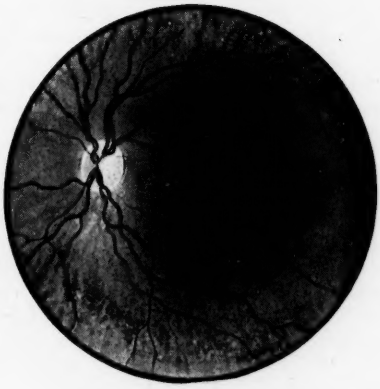
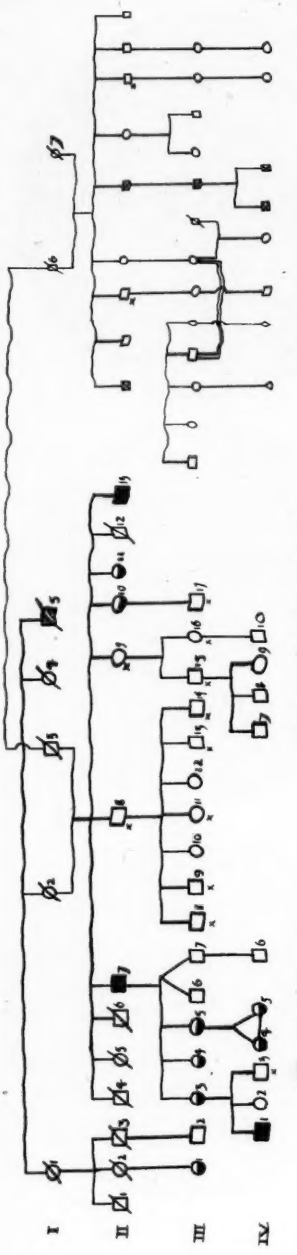


FIG. 6.—Left fundus of S IV, 14, female, aged 6, daughter of S III, 25 a carrier (Fig. 4) and grand-daughter of S II, 7 a carrier (Fig. 3); she thus represents the third generation of presumed carriers.

FIG. 7.—Right fundus of S IV, 22, female, aged 6, daughter of an affected man, S III, 37 (Colour Plate 1*b* and *c*). Her mother (S III, 36) suffers from retinitis pigmentosa.

any visual trouble, nor was any defective visual acuity demonstrated objectively, except that a dark-adaptation curve carried out on S IV, 19 showed some reduction (Fig. 21).



PEDIGREE CHART 4.—The C. family. *Note:*—C IV 2, should be shown as "normal on examination."

(2) The C. Family (Pedigree Chart 4)

The members of the first generation are all dead.

In the second generation there are six survivors, three men and three women. Two of the men (C II, 7 and 13) are affected, and two of the women (C II, 10 and 11) show ophthalmoscopic anomalies.

In the third generation there are no affected men, but four women with ophthalmoscopic lesions were observed (C III, 1, 3, 4, and 5).

In the fourth generation there is an affected man (C IV, 1) and twin girls (C IV, 4 and 5) with ophthalmoscopic anomalies.

In all, therefore, three affected men and eight women with ophthalmoscopic anomalies have been observed in this group. The personal details are shown in the Appendix and are summarized in the legends to the relevant illustrations.

Ophthalmoscopic Appearances and Subjective Symptoms in the Men.—Figs 8 and 9, and Colour Plate 1(*e*) show appearances in the two affected brothers, aged 72 and 56 (C II, 7 and 13), and in the 18-year-old grandson (C IV, 1) of the elder brother. Here, too, there is objective evidence of the progressive nature of the affection, for Fig. 10 shows C II, 13 thirteen years previously. The subjective symptoms in C II, 7 and 13 differ in no way from those seen in the first family, but the youngest patient (C IV, 1) is as yet not conscious of any abnormality. In fact, ophthalmoscopically and subjectively, he fits much better with the women of the group than with the men.

Ophthalmoscopic Appearances in the Women.—These are shown in Fig. 11, Colour Plate 2(*b*), Fig. 12, Colour Plate 2(*f*) and 2(*d*), and Fig. 13, for six individuals whose ages range from 65 to 14 years; in two cases (C II, 11 and C III, 1) no drawing could be made but their fundi showed no marked differences from those observed in the other women. In this family, too, the women were not conscious of any subjective defect, nor could such defects be shown objectively.

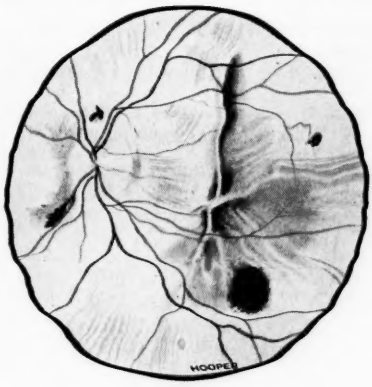


FIG. 8.—Left fundus of C II, 7, male, aged 72, who was first seen in 1938, when vision was 6/9 in each eye with some contraction of the field. The subjective symptoms of nightblindness and restricted field were so mild that he was hardly handicapped. When he was seen again in 1951, 13 years later, vision was reduced to perception of light, and it was found that he had continued at work until shortly after the 1938 examination, when vision had begun to decline rapidly.

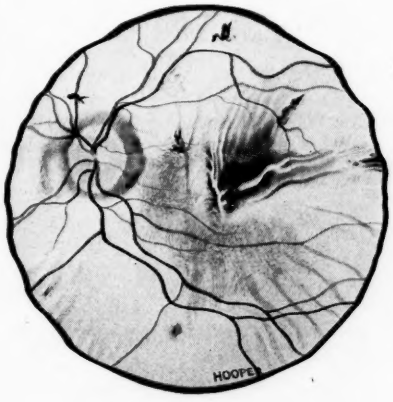


FIG. 9.—Left fundus of C II, 13, male, aged 57, brother of C II, 7 (Fig. 8). Though he is 15 years younger than his brother, the anomalies are almost as advanced. The patient has been conscious of nightblindness all his life, and has had serious visual trouble since the age of 25. When seen in 1938 at the age of 44 (*see* Fig. 10) his vision was 6/24 in the right eye, and 6/6 in the left, with fields reduced to the fixation point. Vision had declined steadily since, and is now only perception of light in the right eye, and 2/60 in the left.

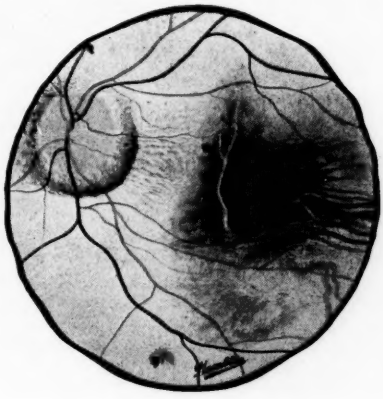


FIG. 10.—Left fundus of C II, 13, when first seen, aged 44, in 1938. Comparison with Fig. 9 shows the deterioration that has occurred over 13 years.

FIG. 11.—Left fundus of C II, 10, female, aged 65, a sister of two affected men, C II, 7 and 13 (Figs 8-10). When first seen in 1938 her vision was 6/9, and her fundi "suggestive of an old central choroiditis". There has been no subjective deterioration, and there is no nightblindness.

FIG. 12.—Left fundus of C III, 4, female, aged 41, a younger sister of C III, 3 (Colour Plate 2*b*). The anomalies are rather more marked than in the elder sister.

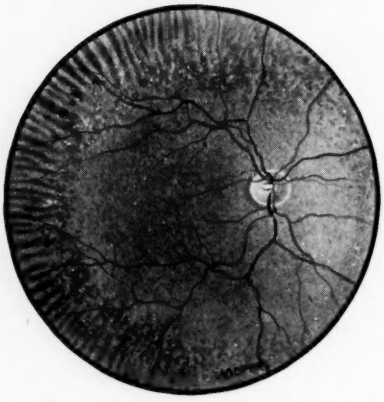
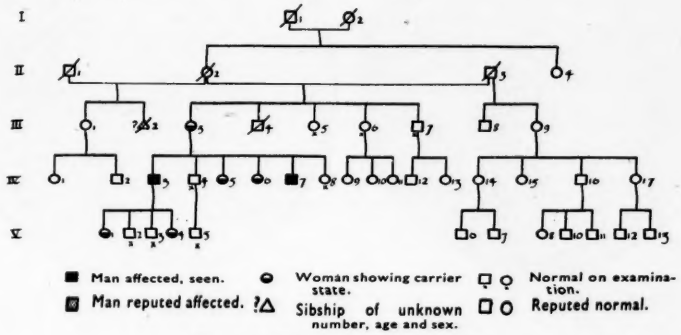


FIG. 13.—Right fundus of C IV, 5, female, aged 14, twin sister of C IV, 4 (Colour Plate 2*d*).

[It is to be noted that a collateral branch of the family suffers from an incomplete and progressive form of day blindness. This affection appears to be unrelated to choroideremia, both by its mode of inheritance and by its symptomatology. An account of this, as yet, incompleted study will be reported in a subsequent communication.]

(3) The G. Family (Pedigree Chart 5)

Ophthalmoscopic changes were observed in three generations, as can be seen from Pedigree Chart 5. There were two affected men (G IV, 3 and 7) and five women (G III, 3; G IV, 5 and 6; G V, 1 and 4) with asymptomatic ophthalmoscopic anomalies.



PEDIGREE CHART 5.—The G. family.

Ophthalmoscopic Appearances and Subjective Symptoms in the Men.—Colour Plate 1(*d*) and Fig. 14 show the fundus appearances in two brothers (G IV, 3 and 7), aged 35 and 25. The elder brother has 6/9 vision, and the younger 6/5, but both are conscious of visual disturbances.

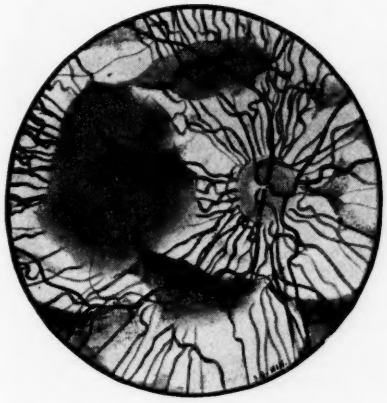


FIG. 14.—Left fundus of G IV, 7, male, aged 25, brother of G IV, 3 (Colour Plate 1*d*). Note that the retina is intact over a considerably larger area than in his brother who is 10 years older. Vision is 6/5, but the field is greatly affected (*see* Fig. 20*a–d*).

The elder brother (G IV, 3) first became conscious of visual disturbances at about the age of 20. He has a low hypermetropic error (right, +1.00 D. sph ⊃ +0.50 D. cyl; left, +1.50 D. sph ⊃ +0.50 D. cyl). His colour vision tested by Ishihara plates is normal. His dark adaptation is markedly abnormal for rod vision (Fig. 22*e*). His field of vision is intact centrally and at the extreme periphery (Fig. 19*a* and *b*, overleaf).

The younger brother (G IV, 7) was kindly seen for us by Mr. Ronald F. Lowe of Melbourne, who reported that the patient had become vaguely conscious of night-blindness at the age of 17. He has hypermetropia of 2.00 D. in the right eye, and 3.75 D.

FIG. 15.—Left fundus of G III, 3, female, aged 56, mother of two affected sons, G IV, 3 and 7 (Colour Plate 1*d* and Fig. 14).

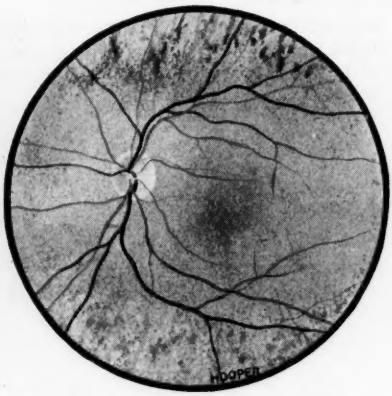


FIG. 16.—Left fundus of G IV, 5, female, aged 31, daughter of G III, 3 (Fig. 15).

FIG. 17.—Left fundus of G IV, 6, female, aged 28, another daughter of G III, 3 (Fig. 15).

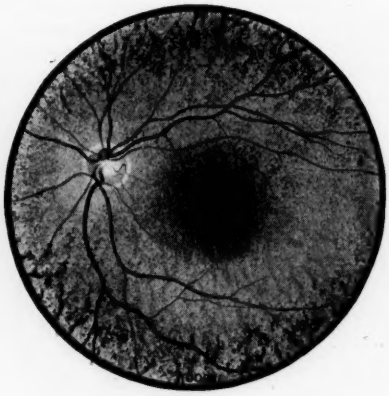


FIG. 18.—Left fundus of G V, 1, female, aged 8, daughter of G IV, 3 (Colour Plate 1*d*). Note the heavy peripheral involvement which is very similar to that seen in G V, 4 (Colour Plate 2*c*).

in the left. His field of vision is more patchily affected than that of his brother (Fig. 20*a–d*, opposite).

Ophthalmoscopic Appearances in the Women.—Figs 15, 16, 17, 18, and Colour Plate 2(*c*) show the ophthalmoscopic appearances in the five affected women (G III, 3; G IV, 5 and 6; G V, 1 and 4) whose ages ranged from 56 to 3½ years. The three adults had no subjective symptoms, and the two children appeared to have none. The observations are set out in Table II (overleaf). Curves of dark adaptation are shown in Fig. 22(*a–d*) which may be contrasted with Fig. 21.

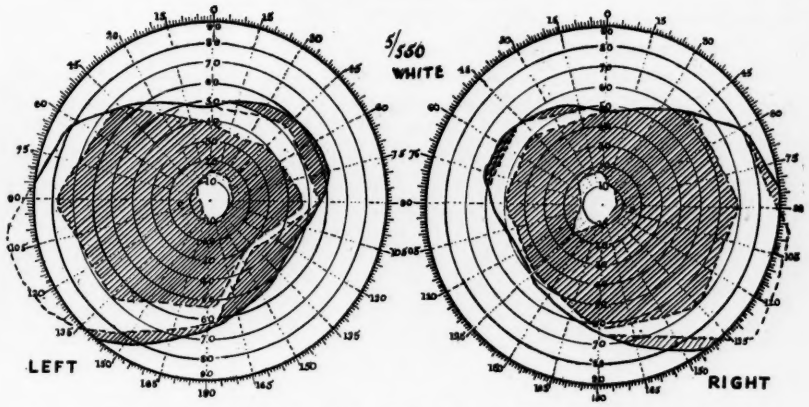


FIG. 19(*a* and *b*).—Peripheral fields of G IV, 3 (Colour Plate 1*d* and Pedigree Chart 5).

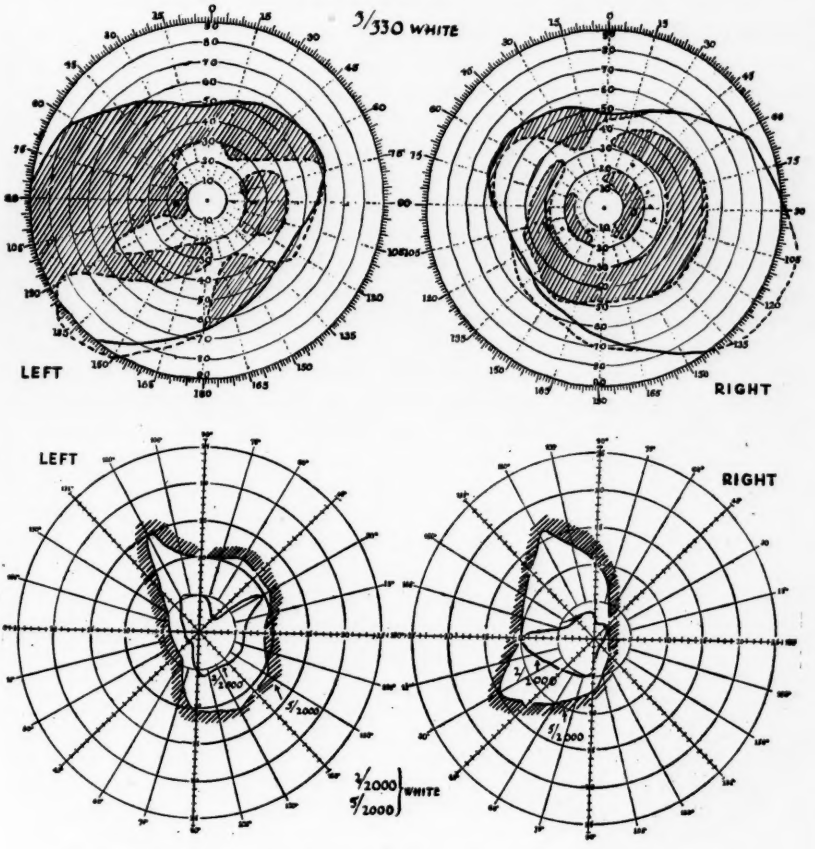


FIG. 20(*a–d*).—Peripheral and central fields of G IV, 7 (Fig. 14 and Pedigree Chart 5), kindly taken by Mr. R. F. Lowe (*Melbourne*).

TABLE II

OBSERVATIONS IN FIVE WOMEN OF THE G. FAMILY

Patient	Refraction	Colour Vision (Ishihara)	Dark Adaptation	Visual Fields	Age
G III, 3	R. and L. +5.0 D. sph. $\bar{c}$ +0.5 cyl.	Normal	Normal	—	56
G IV, 5	R. and L. +1.5 sph.	Normal	Reduced rod curve (? due to pregnancy)	—	31
G IV, 6	R. +2.5 sph. L. +3.0 sph.	Normal	Normal	Central fields normal	29
G V, 1	R. and L. +0.5 sph. $\bar{c}$ +1.0 cyl.	Normal	Normal	—	8
G V, 4	R. and L. Emmetropic	—	—	—	3

Discussion

(1) PROGRESSIVE CHARACTER OF THE AFFECTION IN MEN.—As already indicated, one member of each of the first two families had previously been recorded as an isolated instance of an unusual form of choroideremia: one (S III, 37; Pedigree Chart 3) as a case of partial choroideremia, and the other (C II, 13; Pedigree Chart 4) as a case of choroidal sclerosis in an advanced stage, simulating choroideremia. The original findings 13 years ago in these two cases are shown in Colour Plate 1(*c*) and Fig. 10 respectively. Since that time the true nature of the affection has become obvious, as can be seen from Colour Plate 1(*b*) and Fig. 9, both of which illustrate typical advanced choroideremia. In the first case there was originally little evidence of choroidal sclerosis (Colour Plate 1(*c*)); but in the second case (Fig. 10) the evidence for choroidal sclerosis was rather more definite. It is clear from a comparison of the earlier and the later stages that choroideremia is a progressive affection in which the choroidal vessels become unmasked and sclerosed before they disappear ophthalmoscopically. The appearances of partial choroideremia and of choroidal sclerosis are therefore not, as previously suggested, unusual forms of choroideremia, but merely intermediate stages. The very early stages are still less pathognomonic, as can be seen in Colour Plates 1(*f*) and 1(*e*), which recall the appearances seen in the women of the affected families rather than incipient choroideremia.

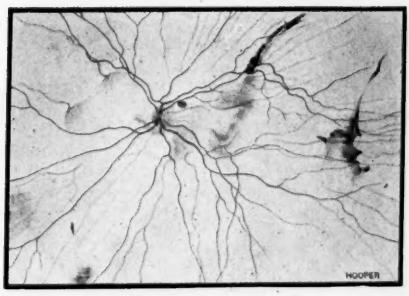
Though the affection is progressive, it bears no direct relationship to age. Though generally more advanced in the elderly, it may yet be fully developed in a relatively young man and only partially so in an older man. In this series, Colour Plate 1(*b*) illustrates a severe stage at the age of 41.

In the course of the affection, some features are prominent:

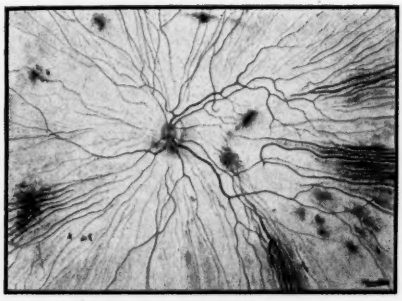
(*i*) It is only towards the end that the reddish central area is engulfed.

(*ii*) Towards the periphery the adjoining edges of normal and damaged tissue generally take the shape of an irregular map-like contour line.

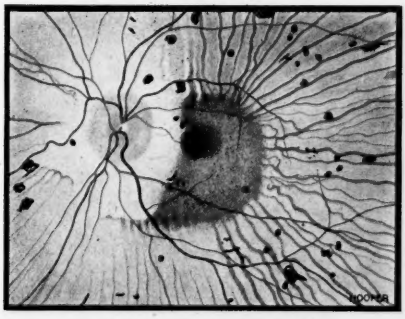
1(*a*).—Right fundus of S III, 32, male, aged 57. Extensive atrophy of choroid. Remnants of choroidal vessels seen temporally, and island of retained red reflex present above. Patient is myopic and conscious of defective vision since childhood; deterioration steady.



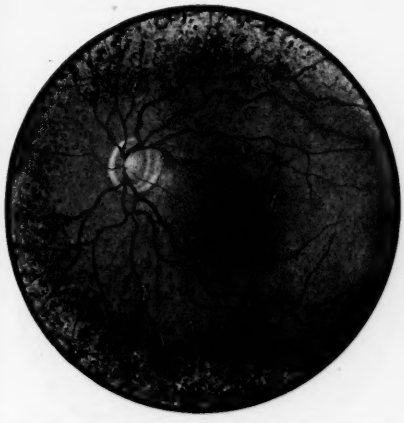
1(*b*).—Left fundus of S III, 37, male, aged 41. Extensive atrophy of retina and choroid. Remnant of retained choroid seen at left of central area. Nightblindness since childhood with progressive deterioration; vision is perception of light only.



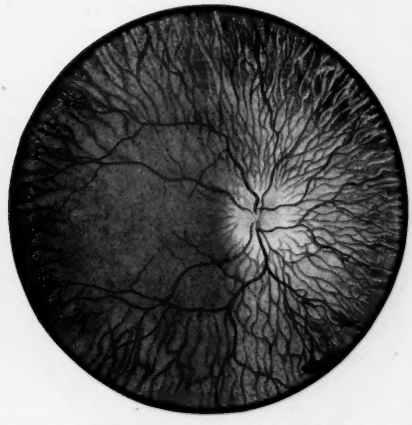
1(*c*).—Left fundus of S III, 37 (earlier stage of 1*b*), showing appearances observed 13 years previously, when the patient was aged 28 and vision was 3/60. The right eye showed an essentially similar picture.



1(*d*).—Left fundus of G IV, 3, male, aged 35. Note retained central fundus area and golden ring of relatively intact retina around disk. Vision 6/9 in each eye, but fields greatly reduced (Fig. 19*a–b*).

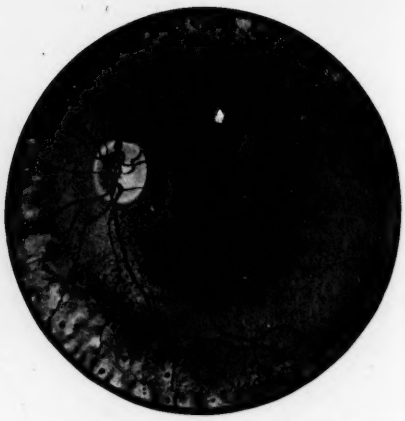


1(*e*).—Left fundus of C IV, 1, aged 18, grandson of C II, 7 (Fig. 8). No nightblindness, vision with correction 6/9. His fundi recall the anomalies seen in carrier women, the appearances being less marked than in his mother (C III, 3, 2*b*).



1(*f*).—Right fundus of S IV, 3, male, aged 4½. His mother (S III, 6, Fig. 5) has noticed that he does not see well in the dusk. Note exposure of choroidal vessels with slight atrophy around disk, and fine pigmentary mottling peripherally.

2(*a*).—Right fundus of S IV, 19, female, aged 23. Besides the characteristic peripheral pigmentation there is a marked central reaction which does not affect vision.

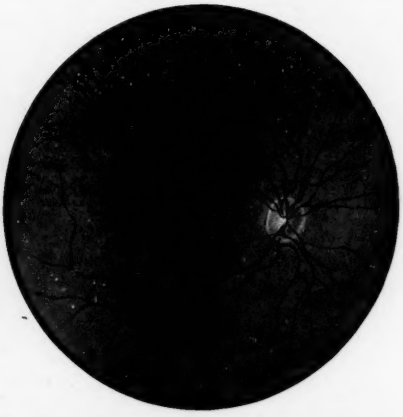


2(*b*).—Left fundus of C III, 3, female, aged 45, eldest daughter of C II, 7 (affected man, Fig. 8).

2(*c*).—Left fundus of G V, 4, female, aged 3½, daughter of G IV, 3 (1*d*). Heavy peripheral involvement very similar to that of her elder sister (G V, 1, Fig. 18).

2(*d*).—Right fundus of C IV, 4, aged 14, daughter of C III, 5 (carrier, 2*f*), and grand-daughter of C II, 7 (affected man, Fig. 8). Appearances in identical twin sister, C IV, 5, are shown in Fig. 13.

2(*e*).—Left fundus of S II, 16, female, aged 65, cousin of S II, 1 (affected man, Fig. 1), and mother of S III, 37 (affected man, 1*b* and 1*c*). Two of her nephews (S III, 32, (1*a*) and S III, 33) are also affected.



2(*f*).—Right fundus of C III, 5, female, aged 39, younger sister of C III, 3 (2*b*) and C III, 4 (Fig. 12). Appearances much less marked than in the other two sisters.

(*iii*) Some relatively healthy tissue tends to remain like a golden halo around the disk until towards the very end. This is seen in Colour Plates 1(*c*) and 1(*b*), and Figs 1, 8, and 9, and is especially marked in Colour Plate 1(*d*) and Fig. 10.

(2) STATIONARY CHARACTER OF THE AFFECTION IN WOMEN.—There is no actual evidence that the fundus changes in women remain stationary, for there is no record of any woman who has been followed-up critically for some years. It may, however, be assumed that the condition is essentially stationary in women for two reasons:

(*i*) There is nothing to suggest that symptoms develop in women later in life. This series includes three women, aged 60 or over, who, though they show substantial ophthalmoscopic changes (Colour Plate 2(*e*) and Figs 2 and 11), are free from any subjective symptoms.

(*ii*) A less cogent reason, there is no relationship between the fundus appearances and the age of the women carriers. In fact, in this series, some of the most marked ophthalmoscopic features were seen in two little girls aged 8 and 3½ (Fig. 18 and Colour Plate 2(*e*)). Furthermore, in a woman aged 55 (Fig. 3), in her daughter aged 31 (Fig. 4), and in her grand-daughter aged 6 (Fig. 6), the appearances are fairly similar. Probably the most marked changes of all were seen in women aged 41, 28, and 23 (Figs 12 and 17 and Colour Plate 2(*a*)).

(3) RANGE OF MANIFESTATIONS

(a) In Men.—Colour Plate 1(*a–f*) and Figs 14, 10, 1, 8, and 9 may be taken as illustrative of the range of ophthalmoscopic appearances in men. On the whole the range follows a chronological order, but not strictly so, for a most severe reaction (Colour Plate 1(*b*)) was found in a man aged 41.

(*i*) *Earliest Stages.*—Colour Plate 1(*f*) shows the earliest stage, observed in a boy aged 6½; here there is little more than some peripheral atrophic reaction with exposure of choroidal vessels. Colour Plate 1(*e*) shows rather more marked changes observed in a boy aged 18.

(*ii*) *Intermediate Stages.*—Colour Plate 1(*c*) shows appearances at the age of 28; here there is exposure of the choroidal vessels with considerable atrophy in between. Somewhat similar appearances are shown in Colour Plate 1(*d*) and Fig. 14. In Fig. 10 choroidal sclerosis approaching the stage of disappearance of the choroidal vessels is in evidence at the age of 43.

(*iii*) *Advanced Stages.*—The diagnosis in Fig. 1, observed in a man aged 67, is now undoubted. Figs 8 and 9 and Colour Plates 1(*a*) and (*b*) represent the most severe phases observed in this series, at the ages of 72, 57, 57 and 41 respectively.

It would seem that the earliest phases show nothing characteristic and do not differ greatly from the appearances seen in carrier women. The subsequent developments are not as yet fully elucidated. Exposure of the choroidal vessels probably occurs relatively early, but conversion of these vessels into white streaks appears to be exceptional. Instead they slowly disappear, the process spreading from the periphery towards the centre with retained islands here and there. The fundus reflex assumes a yellowish

coloration and ultimately ends in the dead white reflex seen in the advanced stage. Complete disappearance of all the choroidal vessels, so that no vestige of the choroidal circulation remains, is apparently exceptional.

(b) In Women.—Here the range is more limited, though it is sufficiently wide to have been reported in the literature under such varying appellations as superficial atrophy of the choroid, pepper and salt fundus, and typical or atypical retinitis pigmentosa. Schematically the appearances may be classified into three groups:

(*i*) *Exclusively Peripheral Disturbances.*—These are illustrated by Colour Plates 2(*f*) and (*b*). In the first there is very mild peripheral disturbance of the pepper and salt type, and in the second the peripheral disturbance is of a gross pigmentary type overlying a pepper and salt reaction. Both these women were mothers of affected children.

(*ii*) *Peripheral Involvement wih Mottling of the Central Areas.*—This is seen in most cases (Colour Plate 2(*e*) and (*c*) and Figs 3, 4, 6, 7, 13, 15, 16, 17, and 18). In some the peripheral involvement is mild (Colour Plate 2(*e*) and Figs 4, 6, 3, and 13). In others the periphery is more heavily affected; succeeding degrees of severity are shown in Figs 16, 7, 15, 17, and 18, and Colour Plate 2(*c*)).

(*iii*) *Peripheral Involvement with Considerable Central Involvement going beyond the Stage of Mottling.*—This is shown in a progressive series in Figs 2 and 11, Colour Plate 2(*d*), Figs 5 and 12, and Colour Plate 2(*b*). There is no relationship between the severity of the peripheral reaction and that seen centrally. A particularly marked central reaction is seen in Colour Plate 2(*a*).

(4) Subjective Symptoms and Refraction

(a) In Men.—The pointing symptom in choroideremia is nightblindness. In the present series, the mother of the boy aged 6½, whose fundi are shown in Colour Plate 1(*f*), had noted that the boy stumbled over things in poor light. In contrast, the young man aged 18, whose fundi are shown in Colour Plate 1(*e*), was not conscious of nightblindness. Likewise in the G. family, two brothers, now aged 35 and 25 respectively, were not conscious of night-blindness in childhood, and the symptom appeared only at the ages of 20 and 17 respectively. At what age defects in the visual fields became manifest is not known, but in these two men the visual fields were severely involved at the relatively early ages at which they were seen (Colour Plate 1(*d*) and Fig. 14). In all cases central vision remains good after the fields are grossly involved, but is ultimately lost. The symptoms are, in fact, not unlike those seen in retinitis pigmentosa—as is shown objectively by the dark-adaptation curve of the elder of the two brothers in the G. family (Fig. 22*e*, overleaf).

It would appear that choroideremia only rarely advances so rapidly that central vision suffers markedly early in life,—as in the case of S III, 37, who was blind by about the age of 25. It is probably true that in most cases blindness does not set in until about the age of 40.

In his analysis of the literature, Waardenburg (1942) suggested that an excess of refractive errors of the low myopia type is to be found in affected men. This reading would have to be evaluated against the incidence of

refractive errors in the normal members of families with choroideremia. In the present series, as can be seen from Table III, almost every type of refractive error (as well as emmetropia) was observed in the affected men in whom refraction was determined.

TABLE III

REFRACTION IN AFFECTED MEN

Patient	Age	Right Eye	Left Eye
S II, 1	67	Not determined	Not determined
S III, 32 ...	57	−7.50 D. sph.	−7.50 D. sph.
S III, 33 ...	55	Not determined	Not determined
S III, 37 ...	41	−7.00 D. sph. c̄ −1.00 D. cyl. 60°	−8.00 D. sph. c̄ −2.00 D. cyl. 90°
S IV, 3	6½	Emmetropic	Emmetropic
C II, 7	72	Emmetropic	Emmetropic
C II, 13 ...	56	−0.50 D. sph. c̄ −1.50 D. cyl. 90°	−0.50 D. sph. c̄ 1.50 D. cyl. 90°
C IV, 1	18	−1.50 D. sph.	−1.50 D. sph.
G IV, 3 ...	35	+1.00 c̄ +0.50 D. cyl. 45°	+1.50 D. sph. c̄ +0.50 D. cyl. 45°
G IV, 7 ...	25	+2.00 D. sph.	+3.75 D. sph.

(b) In Women.—The present study confirms that the carrier state, though ophthalmoscopically fairly obvious, is asymptomatic. The dark-adaptation curves were fully normal in three carrier women examined (Figs 22*a–c*, overleaf) and doubtfully pathological in two (Figs 22*d* and 21, overleaf).

(5) DIFFERENTIAL DIAGNOSIS.—The fully developed picture of choroideremia is pathognomonic, but in the earlier stages the affection presents a considerable diagnostic puzzle. How difficult the diagnosis in women carriers may be is obvious from the discussion of the range of appearances seen in such women. Without a full family history the diagnosis of choroideremia during the early and middle stages, and of the carrier state, must frequently remain problematic. It is also not unlikely that the affection is not so rare as is generally believed.

(6) PATHOLOGY.—Excluding the doubtful case of Fornes Peris (1947), our knowledge of the affection is confined to a report on two cases by McCulloch and McCulloch (1948). As already indicated, there is histological evidence not only of the disappearance of the choroidal vessels but also of sclerosis of these vessels. This conforms to the clinical observations that sclerosis of the choroidal vessels may be seen ophthalmoscopically during the early and middle stages of the affection.

(7) MODE OF INHERITANCE.—The following are the criteria for intermediate sex-linkage:

(*i*) only men are fully affected;
(*ii*) all their daughters show a modified form of the disturbance;
(*iii*) all their sons are unaffected;

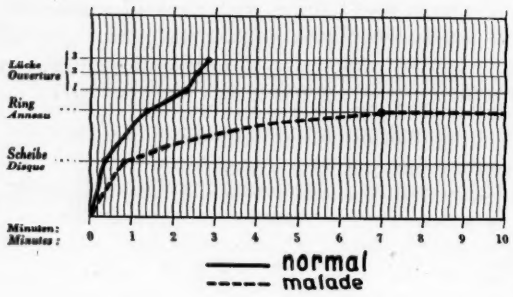


FIG. 21.—Dark-adaptation curve (Della Casa Adaptometer) of a woman carrier aged 23 (S IV, 19 in Pedigree Chart 3). This curve, like that in Fig. 22*d*, shows some reduction in contrast with the normal curves obtained in three women carriers of the G family (Fig. 22*a–c*).

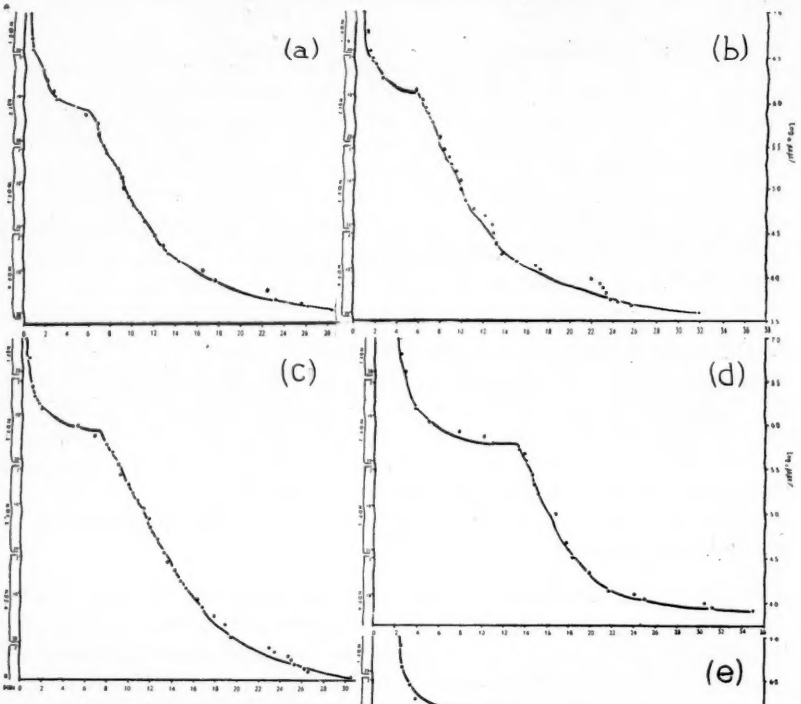


FIG. 22(*a–e*).—Dark-adaptation curves (Crookes Adaptometer) in members of the G family.
(*a*), (*b*), and (*c*).—Normal curves in three carrier women:
(*a*) grandmother (G III, 3, Fig. 15);
(*b*) daughter (G IV, 6, Fig. 17);
(*c*) grand-daughter (G V, 1, Fig. 18).
(*d*) Curve showing reduced rod function in a carrier woman (G IV, 5, Fig. 16); daughter of G III, 3. The abnormality may be physiological owing to pregnancy.
(*e*) Markedly abnormal curve in an affected man (G IV, 3, proband, Colour Plate 1*d*) son of G III, 3. There is some anomaly in the cone component of the curve; the rod component is grossly abnormal.

(*iv*) fifty per cent. of the sons of the carrier daughters are affected, and 50 per cent. of daughters are likewise carriers.

(*v*) no unaffected man transmits the affection, nor does any woman free from the stigmata of the carrier state;

(*vi*) there should be twice as many carrier women in the population as affected men.

Applying these criteria *seriatim* to the families studied here and recorded in Pedigree Charts 3 to 5, the following observations are valid:

(*i*) *Only men are fully affected.*

This applies, except that it is necessary to appreciate that choroideremia is a progressive affection, and that the early stages—as already indicated—differ markedly from the end stage of the affection, and are not easy to diagnose.

(*ii*) *All daughters of an affected man show the carrier state.*

In the S family there are three affected men (S II, 1; S III, 33; and S III, 37) with daughters. In the C family there is one affected man (*C II*, 7) with three daughters. In the G family there is one affected man (G IV, 3) with two daughters. In all there were five men with eleven daughters. Of these eleven women, only eight could be seen, and they all showed the carrier state (Figs 5, 7, 12, and 18, and Colour Plate 2 (*a*, *b*, *c*, *f*), and all but one had affected children (Table IV).

TABLE IV

CHILDREN BORN TO WOMEN SHOWING OPHTHALMOSCOPIC CHANGES

Parents	Children					
	Affected Men or Carrier Women		Unaffected		Not Known	
	M	F	M	F	M	F
S II, 7	—	1	1	—	—	—
S II, 16	1	—	2	—	—	—
S III, 6	1	—	—	—	1	—
S III, 25...	—	1	1	—	—	—
	2	2	4	0	1	0
C II, 10	—	—	1	—	—	—
C III, 3	1	—	1	1	—	—
C III, 5	—	1*	—	—	—	—
	1	1*	2	1	—	0
G III, 3	2	2	1	1	—	—
Total ...	5	5*	7	2	1	0

*An identical twin counted as one.

(*iii*) *All sons of affected men are unaffected.*

Five affected men in these three families had eight sons; of these eight sons only four could be seen, but they were all normal. (The remaining four are reputed normal.)

(*iv*) *Fifty per cent. of sons of carrier women are affected, and 50 per cent. of daughters of carrier women are carriers.*

These families included nine observed carrier women with children. The findings in their children are shown in Table IV. Excluding the one son who could not be seen, there were five affected sons in a total of twelve, and five carrier daughters in a total of seven—a distribution consistent with the theoretical expectation of 1: 1.

(*v*) *No unaffected man transmits the affection, nor does any woman free from the stigmata of the carrier state.*

In these families there is no instance of a normal individual passing on the affection.

(*vi*) *There is a ratio of 2 : 1 of women carriers: affected men.*

The mathematical expectation that in the population there would be twice as many carrier women as affected men arises from the fact that a woman has two chances of having an abnormal X chromosome to a man's one chance. In these families eleven affected men were observed. In contrast there were 21 observed women carriers. (It should however be pointed out that there were three daughters of affected men who could not be seen and who would presumably be carriers: S III, 1, 2, and 5.)

The evidence for intermediate sex-linkage is therefore conclusive. It may be noted that in these pedigrees there are five instances of observed transmission over three generations.

In the S family an affected man (S II, 1) has passed the affection to his grandson (S IV, 3) through his carrier daughter (S III, 6), whilst a carrier woman (S II, 7) has passed the carrier state on to her daughter (S III, 25) and grand-daughter (S IV, 14). The grandmother's first cousin (S II, 16) has transmitted the affection to one of her sons (S III, 37) and through him the carrier state to his daughter (S IV, 22).

In the C family, a man (C II, 7) has passed the carrier state on to his three daughters (C III, 3, 4, and 5), one of whom (C III, 3) has transmitted the affection to a son (C IV, 1), while another (C III, 5) has transmitted the carrier state to her twin daughters (C IV, 4, and 5).

In the G family a carrier woman (G III, 3) has two affected sons (G IV, 3 and 7) and two carrier daughters (G IV, 5 and 6), and her elder affected son has two carrier daughters (G V, 1 and 4).

(8) Clinical Implications of Intermediate Sex-Linkage.—In intermediate, as in recessive sex-linkage, observations over at least three generations are necessary to establish the mode of inheritance, though in the case of intermediate sex-linkage observations over two generations may be adequate. With a recessive sex-linked affection, the evidence is convincing if an affected man has affected grandsons through unaffected daughters. It may, however, happen that the affection is carried over two or three generations of women, and that an affected man will appear who has derived his affection not from his grandfather, but from his great-grandfather, or a more remote ancestor.

In a direct line four or more generations would therefore have to be known; actually the key in such cases is the occurrence of the affection in maternal uncles. With intermediate sex-linkage the fact that the women carrier can be identified makes it possible to diagnose the condition by a study of two generations only. An affected man will have a mother who shows the carrier state.

The frequency with which a recessive or intermediate sex-linked affection becomes manifest is considerably less than the frequency observed in dominant autosomal inheritance. In dominant inheritance 50 per cent. of the children of affected individuals are affected in successive generations. With recessive or intermediate sex-linkage the situation is otherwise; it can be visualized in the following scheme postulating idealized families (Fig. 23):

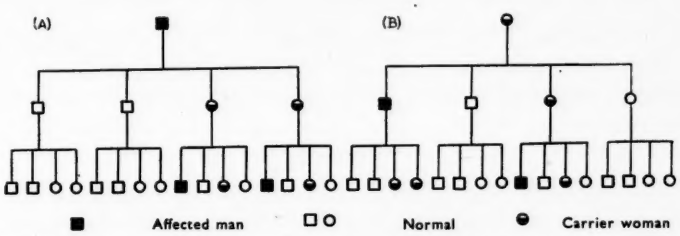


FIG. 23.—Schematic representation of transmission of pathological and carrier states in intermediate sex-linkage in idealized families of four children.
(A) Transmission by an affected man. (B) Transmission by a carrier woman.

In pedigree (A) an affected man has only carrier daughters, and these pass the affection on to 50 per cent. of their sons. In three generations comprising an idealized family group of 21 individuals, there are therefore three affected men.

In pedigree (B) a woman carrier in an identical group has an affected son and a carrier daughter. In the third generation only one boy will be affected. In this idealized family group also comprising 21 individuals there will therefore be two affected men in three generations.

With an autosomal dominant affection, the idealized family group of 21 individuals would give seven affected persons over three generations and there would be no sex distinction.* With an autosomal recessive affection, cases would occur in only one generation, and they would theoretically constitute a quarter of the sibship.

The frequency with which a recessive or intermediate sex-linked affection manifests itself, lies therefore between the frequency given on the one hand by dominant and on the other hand by recessive autosomal affections. Clinically this compels a more exhaustive investigation in a recessive or intermediate sex-linked affection than in either recessive or dominant autosomal affections, in which the family background may be more obvious. In the case of a dominant affection, affected members in the preceding generation

* There would be a sex difference but no numerical difference with dominant sex-linkage; for the purpose of the present discussion this can be ignored.

are more common; in the case of a recessive affection, particularly an uncommon one, consanguinity may be present in a fair proportion of cases.

Intermediate sex-linked inheritance—at any rate in such conditions as choroideremia, where the carrier state is non-pathological—carries this considerable diagnostic advantage over recessive sex-linkage. All the daughters of a man with a recessive or intermediate sex-linked affection are carriers, and genetic advice can be given on the basis of this knowledge. All the daughters of a woman carrier must be regarded as potential carriers in a recessive sex-linked affection, for it is impossible to distinguish the carrier from the non-carrier clinically. In intermediate sex-linkage the carrier can be picked out clinically: in choroideremia the carrier state is betrayed by the ophthalmoscopic changes. Thus any daughters of a carrier woman who have normal fundi can be dismissed from consideration.

(9) NOMENCLATURE.—The term choroideremia is not altogether satisfactory. The name emphasizes the terminal appearances and implies a static condition. Progressive choroidal atrophy would therefore seem to be a more appropriate designation.

Summary

(1) Choroideremia is an affection inherited in an intermediate sex-linked manner, as suggested independently by Goedbloed and Waardenburg (1942), and proved by McCulloch and McCulloch (1948). There is nothing in the older literature that is not consistent with this reading.

(2) An account is given of three families with choroideremia. They all show intermediate sex-linkage. The progressive character of the affection in men is shown by the range of appearances at different ages and by records in two cases re-examined after 13 years. In women, though the ophthalmoscopic changes may be quite marked, there is nothing to suggest that they are progressive, and there are no subjective symptoms.

(3) The clinical implications of intermediate sex-linkage are discussed.

(4) It is suggested that the affection would be better designated " progressive choroidal atrophy ".

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APPENDICES

(1) The S. Family (Pedigree Chart 3)

Generation I

S I, 1 and 2, Mr. and Mrs. L. Dead, reputed normal.
S I, 3, Michel A. Dead, reputed affected.
S I, 4, Berel A. Dead, reputed affected.
S I, 5. Number and sex not known.

Generation II

S II, 1–8. Children of S I, 1 and 2, both reputed normal.

1. *Nathan L.* First seen in 1948, aged 67, affected. Visual acuity: perception of light only. Poor projection. Nightblind since early childhood, and incapacitated since about the age of 55. Fundi showed advanced stage of choroideremia (Fig. 1).

2. *Lewis L.* Died aged 62, reputed normal.

3. *Mrs. Julie P.* Seen February 4, 1951, aged 65. No subjective symptoms. Visual acuity: 6/9 each eye. Fundi: typical carrier, fairly severe changes (Fig. 2). No children.

4. *Mrs. Annie W.* Aged 64, lives in New York, not seen.

5. *Mrs. Katie C.* Seen November 22, 1950, aged 62. Visual acuity: right, 3/60, with −4.0 D. sph. 6/18 or more; left, 3/60, with −3.0 D. sph. 6/18 or more. Fundi: normal except for mild arteriosclerosis.

6. *Mrs. Millie Le.* Seen January 4, 1951, aged 60, no eye trouble. Visual acuity: 6/6 in each eye. Fundi: normal.

7. *Esther B.* Seen October 10, 1950, aged 55. Visual acuity: 6/6 each eye. Fundi: carrier type, mild (Fig. 3).

8. Unknown number and sex. Died young.

S II, 9–10. Children of S I, 3, sex not known.

S II, 11–16. Children of S I, 4, reputed affected.

11, 12, and 13. *Harry, Leon, and Nathan A.* This branch of the family and their descendants were murdered in Nazi concentration camps. They are reputed to have been normal.

14. *Nrs. Nacha T.* 1866–1944, reputed normal.

15. *Mrs. Sarah G.* Dead.

16. *Mrs. Rebecca S.* Seen in 1950, aged 65. Early lens changes both eyes. No subjective symptoms. Fundi: carrier type, medium (Colour Plate 2*e*).

Generation III

S III, 1–6. Children of S II, 1, affected.

1. *Mrs. Gertie C.* Aged 39, could not be seen.

2. *Mrs. Annie V.* Younger sister, could not be seen.

3. *Sidney L.* Seen February 22, 1951, aged 34. Visual acuity: 6/6 each eye. Fundi: normal. Emmetropic.

4. *Harry L.* Seen May 22, 1951, aged 32. Visual acuity: 6/6 each eye. Fundi: normal.

5. *Mrs. Renie D.* Aged 31, could not be seen.

6. *Mrs. M.* Seen in 1950, aged 27. Visual acuity: right, 6/18, with $+4.00 \supset -2.75$ at $175° = 6/9$; left, 6/18, with $+4.00 \supset -2.75$ at $175° = 6/9$. Fundi: carrier type (Fig 5).

S III, 7–12. Children of S II, 2, reputed normal.

7. *Norman L.* Seen December 19, 1950, aged 36. Visual acuity: 6/5 each eye with correction. Fundi: normal.

8. *Harold L.* Seen December 19, 1950, aged 34. Visual acuity: 6/6 each eye. Fundi: normal.

9. *Bernard L.* Seen December 18, 1950, aged 30. Visual acuity: right, 6/36, with correction 6/6; left, 6/60, with correction 6/6. Fundi: normal.

10. *Mrs. M. E. S.* Seen March 3, 1951, aged 28. Visual acuity: 6/6 each eye. Normal colour vision (Ishihara). Fundi: normal.

11. *Miss Irene L.* Seen March 3, 1951, aged 27. Visual acuity: $-2.75 \supset +0.50$ at $180° = 6/5$, each eye. Normal colour vision (Ishihara). Fundi: normal.

12. *Miss Anita L.* Seen March 3, 1951, aged 22. Visual acuity: 6/6 each eye. Fundi: normal.

S III, 13–14. Sons of S II, 4, not traced.

13. *Mr. W.*
14. *Mr. W.* Dead } In U.S.A., not seen.

S III, 15–21. Children of S II, 5, normal.

15. *Ben C.* Aged 35. Visual acuity: right, 6/60; left, 6/36. Lens changes in both fundi similar to those of his brother Percy (S III, 18).

16. *Harry C.* Aged 32. Fundi: normal.

17. *Miss C.* Died young.

18. *Percy C.* Aged 28. Royal Eye Hospital No. 49/1676. First seen in 1948. Poor sight and nightblindness since childhood. Visual acuity: 6/18, each eye. Colour vision normal (Ishihara).

April 6, 1951. Visual acuity: right, 6/18; left, 6/24. Emmetropic. Very slight nystagmus. Object under regard "jumps about". Fundi show a central lesion with evident choroidal sclerosis and patches of choroidal atrophy and pigmentation.

19. *Martin C.* Aged 25, no subjective symptoms. Visual acuity: 6/5. Fundi: normal.

20. *Rose C.* Aged 22. Visual acuity: 6/5 each eye. Fundi: normal.

21. *Maurice C.* Aged 18. Visual acuity: 6/5 each eye. Fundi: normal.

S III, 22–24. Children of S II, 6, normal.

22. *Mrs. Pearl T.* Aged 28. Visual acuity: right, 6/9; left, 6/6. Colour vision normal (Ishihara). Fundi: normal.

23. *Rene Le.* Aged 25. Visual acuity: 6/6 each eye. Fundi: normal.

24. *Harry Le.* Aged 23. Visual acuity: 6/6 each eye. Colour vision normal (Ishihara).

S III, 25–26. Children of S II, 7, a woman showing the carrier state.

25. *Mrs. Sh.* Seen October 3, 1950, aged 31. Visual acuity: right refraction: $+1.50 \supset -4.25$ at $15° = 6/9$; left, $+1.25 \supset -4.25$ at $165° = 6/9$. Fundi: mild carrier type (Fig. 4).

26. *Alfred B.* Aged 29. Visual acuity: 6/6 each eye. Fundi: normal.

S III, 27–30. Children of S II, 11–13, all massacred during the war.

S III, 31–34. Children of S II, 14, all live in Switzerland.

31. *Salomon Tu.* Aged 59. Fundi: normal (Prof. Marc Amsler).

32. *Leon Tu.* Aged 57. Affected. Nightblind since childhood (Colour Plate 1*a*). Refraction -7.5 D. each eye. Left, $\bar{c}$ correction $= 6/60$. Fields greatly reduced. Advanced choroideremia.

33. *Isidor Tu.* Aged 55. Affected. Appearances as in his brother (not drawn).

34. *Max Tu.* Aged 43. Normal (Prof. Amsler).

S III, 35. Children of S II, 15, deceased. Number and sex not known.

S III, 36. Mrs. S. Aged 38, wife of S III, 37, is blind from retinitis pigmentosa. She is unrelated to this family.

S III, 37–39. Children of S II, 16, a woman showing carrier state.

37. *Sid* (*Sole*) *Sch.* Now aged 41. Proband. First seen in 1938, aged 28, and recorded as a case of partial choroideremia without family history (Sorsby, 1940); fundi were then as in Colour Plate 1(*c*). The appearances now, 13 years later, are shown in Colour Plate 1(*b*). He suffered from nightblindness since childhood, but owing to steady deterioration of vision had to give up his work as a tailor at the age

of 18, and has been blind since the age of 25. Vision is now barely perception of light. Refraction: right, −7.00 D.S. ⊂ −1.00 cyl. axis 60°; left, −8.00 ⊂ −2.0 axis 130°.

38. *Mr. Sh.* Seen November 4, 1950, aged 33. Visual acuity: 6/6 each eye. Fundi: normal.

39. *Ben Sa.* Aged 42. Visual acuity: 6/6 each eye. Fundi: normal.

Generation IV

S IV, 1–4. Grandsons of S II, 1, affected.

1 and 2. Not seen.

3. *Howard M.* Affected. Seen January 8, 1951, aged 6½. His mother, S. III, 6, shows the carrier state. His parents have noticed that he collides with objects in the dark. Emmetropic. Fundi: *see* Colour Plate 1(*f*).

4. *Stewart M.* Aged 4½, not seen.

S IV, 5. Daughter of S III, 8, normal. Aged 3 months, not seen.

S IV, 6–7. Children of S III, 10, normal.

6. *David S.* Aged 6. Deaf-mute. Emmetropic. Colour vision normal (Ishihara). Fundi: normal.

7. *Carol S.* Aged 4. Emmetropic. Colour vision normal (Ishihara). Fundi: normal.

S IV, 8. Daughter of S III, 15, not seen.

S IV, 9. Son of S III, 16, not seen.

S IV, 10. Lewis T. Son of S III, 22, normal. Seen April, 1951, aged 9 months. Fundi: normal.

S IV, 11. Son of S III, 24, normal. Reputed normal.

S IV, 12. Miriam B. Seen October 3, 1951, aged 2. Fundi: normal.

S IV, 13–14. Children of S III, 25, a woman showing the carrier state, and her second cousin, S III, 38, normal.

13. *Frank Sh.* Seen October 3, 1950, aged 7. Visual acuity: 6/6 each eye. Fundi: normal, though with a heightened macular reflex.

14. *Charlotte Sh.* Seen October 3, 1950, aged 5. Visual acuity: 6/6 each eye. Fundi: carrier type, mild (Fig. 6).

S IV, 15–16. Children of S III, 31, normal.

15. *Mima Tu.* Aged *c* 34, at Buenos-Aires, not seen, reputed normal.

16. *Moritz Tu.* Aged 32, at Zurich, not seen, reputed normal.

S IV, 17–19. Children of S III, 33, affected.

17. *Raphael Tu.* Aged 27, at Zurich, not seen, reputed normal.

18. *Max Tu.* Aged 25, at Zurich, not seen, reputed normal.

19. *Bertha Lu.* Aged 23. Vision full. Refraction: +3.75 ⊂ +0.50 at 90° each eye. Fields full. Slightly defective dark adaptation (Fig. 21). Fundi: carrier type, severe. (Colour Plate 2*a*).

S IV, 20–21. Children of S III, 34, normal.

20. *Ludwig Tu.* Aged 17, reputed normal.

21. *Harold Tu.* Aged 11, reputed normal.

S IV, 22. Evelyn Sch. Seen December 1, 1950, aged 6. Daughter of S II, 37, himself affected, and of S II, 36, a woman blind from retinitis pigmentosa. Fundi: carrier type, severe (Fig. 7).

S IV, 23–24. Children of S III, 39, normal.

23. *Wallis Sa.* Seen November 4, 1950, aged 16. Refraction: right, −4.00 ⊃ −0.50 at 90° = 6/9; left, −4.00 ⊃ −0.50 at 90° = 6/9. Fundi: normal.

24. *Philip Sa.* Seen November 4, 1950, aged 9. Refraction: right, −1.75 ⊃ −0.50 at 90° = 6/7.5; left, −2.00 ⊃ −0.50 at 90° = 6/7.5. Fundi: normal.

(2) The C. Family (Pedigree Chart 4)

Generation I

C I, 1. Mrs. Sarah H. Died when over 60 years old, reputed normal.

C I, 2. Mrs. Hannah C. Dead, reputed normal.

C I, 3. Mr. C. Husband of Hannah C., dead, reputed normal.

C I, 4. Miss Janie P. Dead, reputed normal.

C I, 5. Mr. George P. Dead, reputed affected.

C I, 6–7. Mr. and Mrs. C. This branch of the family and their descendants will be the subject of a subsequent report.

Generation II

C II, 1–3. Children of C I, 1, herself reputed normal.

1. *Thomas* W. Dead, reputed normal.
2. *Mrs. Caroline Sarah K.* Dead, reputed normal.
3. *John W.* Dead, reputed normal.

C II, 4–13. Children of C I, 2 and 3, both reputed normal.

4. *Thomas C.* Died aged 70, reputed normal.
5. *Edith C.* Dead, reputed normal.
6. *Harold C.* Dead, reputed normal.
7. *Charles C.* Aged 72. Affected. First seen in 1938, when vision was 6/9 each eye (Sorsby, 1939). The subjective symptoms were then so mild that he was barely handicapped (he was, however, an unwilling witness). When seen again in 1951, vision was perception of light in both eyes, and he reported that his sight began to fail at 60. The fundus appearance in 1951 is shown in Fig. 8. Emmetropic.
8. *Arthur C.* Aged 70. Visual acuity: 6/6 each eye, with +2.00 D. sph. Fundi: normal.
9. *Mrs. Nellie We.* Aged 66, was seen by Dr. J. H. Dowds (*Bulawayo*) and reported to be normal.
10. *Mrs. Ada Pr.* Aged 64. First seen with C II, 7 and 13, in 1938. Her vision was then 6/9 and "suggestive of an old central choroiditis". When seen again in 1951, there was probably some extension peripherally (Fig. 11).
11. *Mrs. Rosie A.* Aged 63, was seen by Dr. B. Kay (*Cape Town*). Vision 6/18 each eye, with +1.00 D. sph. 6/9 each eye. No subjective symptoms. Fundi: carrier state.
12. *Ernest C.* Died aged 56, reputed normal.
13. *William A. C.* Aged 57. His sight has always been defective; he has been handicapped since the age of 25, and nightblind ever since he remembers. Refraction: ⊃ −0.50 −1.50 at 90°, each eye. Proband (Sorsby, 1939). In 1937, when he was 44 years old, his vision was 6/24 in the right eye and 6/6 in the left; the fields were reduced to the fixation points. The fundus appearance is shown in Fig. 10.

When seen again in 1948, his vision had declined to right, hand movements, and left, 6/60. Fundus appearance in 1948 is shown in Fig. 9.

Two years later, in 1950, his vision had deteriorated still further to right, perception of light, and left, 2/60.

Generation III

C III, 1. Miss N. K. Aged 61, no subjective symptoms. Visual acuity: 6/9 each eye. Fundi: carrier state.

C III, 2. Mr. W. Whereabouts and age not known, reputed normal.

C III, 3–7. Children of C II, 7, himself affected.

3. *Mrs. Florence F.* Seen April 5, 1951, aged 45. Visual acuity: 6/6 each eye. Colour vision normal. Fundi: carrier state (Colour Plate 2*b*).

4. *Mrs. Doris J.* Aged 41. Visual acuity: 6/6 each eye. Fundi: carrier state (Fig. 12).

5. *Mrs. He.* Seen January 28, 1951, aged 39. Visual acuity: 6/6 each eye. Fundi: carrier state (Colour Plate 2*f*).

6. *Jack C.* Aged 32, no subjective symptoms, emmetropic. Visual acuity: 6/6 each eye. Colour vision normal (Ishihara). Fundi: normal.

7. A twin brother of C III, 6. Reputed normal.

C III, 8–14. Children of C II, 8, himself normal.

8. *Arthur C.* Aged 42. Visual acuity: 6/5 each eye. Fundi: normal.

9. *Henry C.* Aged 41. Visual acuity: 6/6 each eye. Fundi: normal.

10. *Ivy C.* Aged 39, reputed normal.

11. *Florence C.* Aged 33. Visual acuity: 6/6 each eye. Fundi: normal.

12. *Phyllis C.* Aged 32, reputed normal.

13. *Alfred C.* Aged 30. Visual acuity: 6/6 each eye. Fundi: normal.

14. *Frederick C.* Aged 28. Refraction: right, $-0.50 \supset -1.00$ at 90°; left, emmetropic = 6/5. Fundi: normal.

C III, 15–16. Children of C II, 9, herself normal.

15 and 16. Son and daughter, seen and found normal by Dr. D. H. Dowds (*Bulawayo*).

C III, 17. Mr. Pr. Son of C II, 10, a woman showing the carrier state. Aged 27. Visual acuity: 6/9 each eye. Fundi: normal.

Generation IV

C IV, 1–3. Children of C III, 3, a woman showing carrier state.

1. *Douglas B. F.* Aged 18. Affected. Not conscious of nightblindness. Visual acuity: 6/9 each eye, with −1.50 D. sph. Colour vision normal (Ishihara). Fundi: resemble those of a carrier (Colour Plate 1*e*).

2. *May F.* Aged 17. Visual acuity 6/6 each eye. Fundi: normal.

3. *David F.* Aged 14. Visual acuity: 6/6 each eye. Fundi: normal.

C IV, 4–5. Identical twin daughters of C III, 5, a woman showing carrier state.

4. *Barbara He.* Aged 14. Visual acuity: 6/6 each eye. Fundi: carrier state (Colour Plate 2*d*).

5. *Joan He.* A twin sister. Visual acuity: 6/6 each eye. Fundi: carrier state (Fig. 13).

C IV, 6. Son of C III, 7, reputed normal.

C IV, 7–9. Two sons and a daughter of C III, 15, a normal man, reputed normal.

C IV, 10. Son of C III, 16, a normal woman, reputed normal.

(3) The G. Family (Pedigree Chart 5)

Generation I

G I, 1. Mr. H. Died when over 70. No history of any eye trouble, was a gamekeeper and then a Metropolitan policeman.

G I, 2. Mrs. H. No history of any eye trouble. Nothing further known.

Generation II

G II, 1. Mr. S. Died in his thirties. First husband of Mrs. Agnes G. (G II, 2), reputed normal.

G II, 2. Mrs. Agnes G. Died at 64. "Had good sight". One daughter (G III, 3) of her second marriage is a carrier.

G II, 3. Mr. G. Died when over 70. Wore spectacles but had good sight. Second husband of Mrs. Agnes G. (G II, 2).

G II, 4. Mrs. Charlotte C. Possibly still alive but not traced. Nothing known of her sight.

Generation III

G III, 1–2. Children of G II, 2 by her first marriage.

1. *Mrs. Isabella S.* Aged 70. Refraction: right, $+5.75 \bigcirc -1.00$ at $180° = 6/9$; left, $+4.25$ D.S. $= 6/9$. Could not be examined, but when seen some years ago at the London Refraction Hospital (Case No. 14088) changes suggestive of arteriosclerosis were noted. Nothing else in the fundus appearance was remarked upon.

2. There were other children of the first marriage of G II, 2, but these could not be traced.

G III, 3–7. Children of G II, 2 by her second marriage.

3. *Mrs. Mary Ann G.* First seen May, 1951, aged 56. Refraction: $+5.00$ D.S. $\bigcirc +0.50$ at $180° = 6/6$ each eye. Colour vision normal (Ishihara). Fundi: carrier type, medium (Fig. 15). Dark adaptation: normal (Fig. 22*a*).

4. *William G.* Pilot in Royal Flying Corps, killed in the first world war at the age of 26, reputed normal.

5. *Mrs. Nina J.* Seen May, 1951, aged 51. Refraction: right $+1.50$ at $170° = 6/6$; left $+1.00$ at $15° = 6/6$. Colour vision normal (Ishihara). Fundi: arteriosclerotic changes but otherwise normal.

6. *Mrs. Margaret H.* Refraction: $-0.50 = 6/9$ each eye. Colour vision normal (Ishihara). Fundi: normal.

7. *Alfred John G.* Seen August 22, 1951, aged 52. Refraction: right $+5.00 \bigcirc +3.50$ at $90° = 6/9$; left $+4.50 \bigcirc +1.50$ at $90° = 6/9$ partly. Fundi showed arteriosclerotic changes with narrowed vessels and macular changes; the condition was more marked in the left eye and there was evidence of an old macular haemorrhage. Blood pressure 130/80. No evidence of choroideremia. Colour vision normal. Dark-adaptation curve showed a slightly restricted rod curve.

G III, 8–9. Children of G II, 3 by his first marriage.

8. *Albert G.* Not seen, reputed normal.
9. *Mrs. Alice Elizabeth M.* Not seen, reputed normal.

Generation IV

G IV, 1–2. Children of G III, 1, a normal woman.

1. *Daughter.* Married and lives in Canada, whereabouts not known.
2. *Stanley Sm.* Could not be examined, reputed normal.

G IV, 3–8. Children of G III, 3, herself a carrier.

3. *Mr. Albert Charles Ga.* Proband. First seen April, 1951, aged 35. Colour vision normal (Ishihara). Fields of vision: central field about 10° horizontally and 15° vertically, in the extreme periphery there was a band of vision some 5° wide on the nasal side and some 20° wide on the temporal side (Fig. 19*a* and *b*). Dark adaptation: both rod and cone curves abnormal. He found the test difficult because of his very small central field (Fig. 22*e*). Refraction: right, +1.00 ⊂ +0.50 at 45° = 6/9; left, +1.50 ⊂ +0.50 at 45° = 6/9.

He has been aware of his trouble since the age of 20 and recently has had trouble when reading small print. He has been consious of his field restriction since 1939. Fundus appearance shown in Colour Plate 1(*d*).

4. *Mr. Ernest Ga.* Seen April, 1951, aged 33. Refraction: right, +1.50 = 6/6; left, +2.00 ⊂ +1.50at 180° = 6/6. Colour vision normal (Ishihara). Dark adaptation: normal. Fundi: normal.

5. *Mrs. Hilda B.* Seen April, 1951, aged 31. Refraction: +1.50 D.S. = 6/5 each eye. Colour vision normal (Ishihara). Dark adaptation: rod curve (Fig. 22*d*) very reduced but this was attributed to her being pregnant. Fundi: carrier type, medium (Fig. 16).

6. *Miss Olive Ga.* Seen April, 1951, aged 29. Visual fields, central and peripheral normal. Fundi: carrier state (Fig. 17). Dark adaptation: normal (Fig. 22*b*). Refraction: right, +2.50 D.S. = 6/6; left, + 3.00 D.S. = 6/6.

7. *Mr. Wilfred Ga.* Affected. Seen by Mr. R. F. Lowe (*Melbourne*) in May, 1951, aged 25. Refraction: right, +2.50 ⊂ −0.50 at 180° = 6/6; left, +3.75 D.S. = 5/6. "He had no trouble with his eyes until 17, when he found his vision for fine print failing". This later improved but about 4 months ago he found that during his work as a piano tuner he would lose detail when peering at things inside the piano. This was only a transient phenomenon and passed off after a few seconds. Some difficulties with night vision appear to go back to this period. Colour vision was not taken but the patient made no mention of being colour blind. Visual fields: right eye (Fig 20*a* and *c*) shows annular scotomata with upper nasal peripheral erosion, while the central area is spared; left eye (Fig 20*b* and *d*) shows annular scotomata which have broken through to peripheral erosions, while the central area is spared. Fundus appearance shown in Fig. 14.

8. *Miss Mary Ga.* Aged 23. Refraction: +2.50 D.S. = 6/5 each eye. Colour vision normal (Ishihara). Fundi: normal.

G IV, 9–11. Children of unaffected woman (G III, 6), reputed normal.

G IV, 12–13. Children of unaffected man (G III, 7), reputed normal.

G IV, 14–17. Grandchildren of G II, 3 through G III, 9, unaffected daughter of his first marriage, reputed normal.

Generation V

G V, 1–4. Children of G IV, 3, an affected man (Proband).

1. *Ann Marie Ga.* Seen May, 1951, aged 8. Refraction: +0.50 ⊂ 1.00 at 120° = 6/5 each eye. Colour vision normal (Ishihara). Dark adaptation: normal (Fig. 22*c*). Fundus: carrier type (Fig. 18).

2. *Norman Joseph Ga.* Aged 6. Refraction; +1.00 = 6/6 each eye. Colour sense slightly depressed but no definite anomaly detectable. Fundi: normal.

3. *James Kanice Ga.* Aged 5. Refraction: +1.50 = 6/6 each eye. Fundi: normal.

4. *Dorothy Theresa Ga.* Aged 3. Emmetropic. Fundi: carrier type (Colour Plate 2*c*).

G V, 5. Michael G. Aged 6. Colour vision normal. Fundi: normal.

G V, 6–12. Great-grandchildren of G II, 3 by his first marriage, reputed normal.

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ELECTRON-MICROSCOPIC STUDY OF CHLAMYDOZOON TRACHOMATIS*†

BY

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NOTHING is known with certainty regarding the electron-microscopic finding of the trachoma virus, *Chlamydozoon trachomatis*. Trials to demonstrate the virus by means of the electron microscope have been made by several Japanese investigators during the past few years. The only finding with a suspicious virus shadow, however, was that obtained by Itô and others (1951), and that obtained by one of us (Tsutsui, 1951).

It was then supposed by another of the present authors (Y. M.) that the failure might have been due to an inadequate selection of conjunctival materials. It is not easy to get more than 100 mg. of conjunctival tissue from a single case of trachoma; in addition, the causative agent is believed to exist only in the epithelial layer of this tissue. An electron-microscopic examination cannot be performed adequately, therefore, unless materials with the highest concentration of the virus have been used. Inclusion bodies apparently indicate the virus, so that cases with innumerable inclusions should be used for the investigation, but despite the high trachoma index in Japan such cases are comparatively rare.

A few such cases were encountered in the course of a study of the mass treatment of trachoma with terramycin (Mitsui, Tanaka, and others, 1951). The material was sent for electron-microscopic examination to the third author (J. T.) together with some control material in 50 per cent. glycerol.

FIG. 3.—Inclusion bodies in a scraping slide. Arrow indicates early-stage colony of the virus developed from a single mother element.

Electron-Microscopic Identification of Trachoma Virus

The findings in all these cases were uniform, the electron micrographs from Case 1 being the most distinct (Figs 1 and 2). The virus appeared more or less round in shape, but some elongated virus individuals, suggesting a pre-division stage, also occurred. The size varied widely between about 80 and 350 millimicrons.

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FIG. 1.—Electron micrograph from Case 1 (× 20,000).

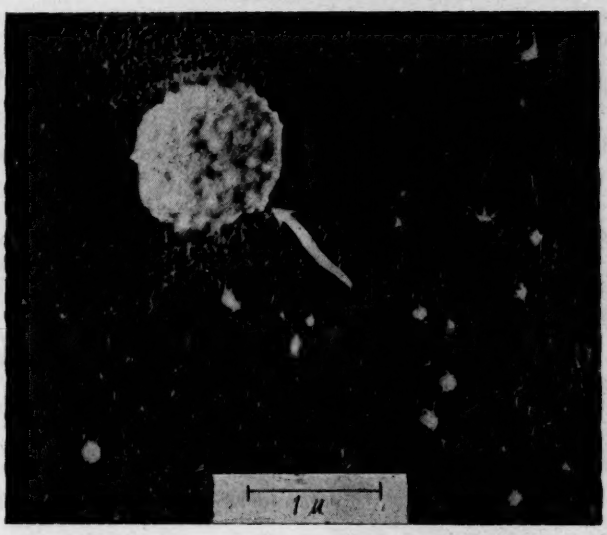

FIG. 2.—Electron micrograph from Case 1. Arrow indicates early-stage colony or morula (× 20,000).

The size and form of the virus appearing in the electron micrograph seem to correspond, so far as the elements in the visible range are concerned, with those of the elementary and initial form of Prowazek's inclusion bodies. A pleomorphism is the criterion which has been considered characteristic of the *Chlamydozoaceae* viruses.

One appearance (Fig. 2, arrow) is of particular interest; it may be compared with those often found in scraping slides (Fig. 3, arrow), and consists of an early-stage

colony of the virus developed from a single mother virus element—the so-called morula or matrix.

These elements were rarely seen in specimens from trachomatous conjunctiva with few inclusion bodies. None of these findings was obtained from any of the control material.

Purification of the Virus

The virus was purified and concentrated by chemical technique according to the procedure recommended by Cox and others (1947):

(*i*) Biopsied conjunctiva emulsified with saline solution (1: 10 dilution).
(*ii*) Emulsion kept in refrigerator for 24 hrs.
(*iii*) Freezing at −11° to −18° C. and melting at 30° C. repeated five times.
(*iv*) Material centrifuged for 30 min. at 4,000 r.p.m.
(*v*) Supernatant fluid mixed with an equal part of ether to eliminate fat substances.
(*vi*) Mixture centrifuged for 30 min. at 4,000 r.p.m. to separate ether.
(*vii*) After separation from ether, supernatant fluid re-centrifuged for 30 min.
(*viii*) 50 per cent. methanol (pure methanol mixed with equal part of phosphate buffer at *p*H 7.0) dropped into fluid until final concentration of methanol became 25 per cent.
(*ix*) Mixture kept at −4° C. for 3 hrs (solution opaque).
(*x*) Mixture centrifuged at 4,000 r.m. for 30 min. at 2° C.
(*xi*) Sediment thus obtained refined by phosphate buffer (m/100, *p*H 5.6), *i.e.*, it was added to buffer solution and centrifuged as given in (*x*).
(*xii*) Sediment added to phosphate buffer (m/100, *p*H 7.6). Freezing and melting repeated thrice as in (*iii*).
(*xiii*) Mixture centrifuged at 3,000 r.p.m. for 30 min. at 2° C.

The supernatant fluid then contained the refined virus, and this constituted the final material for electron microscopy.

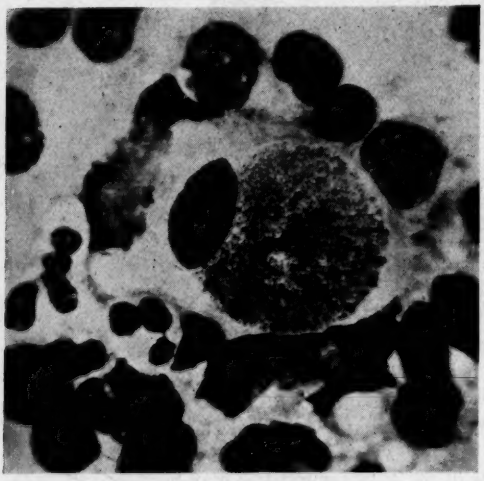

FIG. 4.—Inclusion body in scraping from Case 1.

Conjunctival Materials

Case 1, female, aged 14, with chronic trachoma of about one year's duration, the clinical appearances being most severe. A scraping examination revealed a large number of typical inclusion bodies (Fig. 4). More than ten inclusions were demonstrated histo-pathologically in each section of conjunctiva. Histopathological changes other than inclusions were also typical of trachoma. The upper fornix conjunctiva of the left eye was biopsied for histopathological examination and the lower fornix of the same eye was cut for the electron-microscopic examination. Care was taken to get the latter sample as thin as

possible since the existence of the virus is thought to be limited to the epithelial layer.

Case 2, female, aged 13, chronic trachoma of several years' duration. Clinical and histopathological findings were similar to those of Case 1. The lower fornix conjunctiva of the left eye was used for electron-microscopic examination.

Case 3, female, aged 14, chronic trachoma of several years' duration. Inclusions were most abundant in the scraping. The conjunctivae of both fornices of the left eye were used for the study.

Case 4, male, aged 19, acute trachoma of 3 weeks' duration. The conjunctivae of both fornices of the right eye were used for the examination.

Control Cases.—Several examples of normal conjunctiva, bacterial conjunctivitis, and trachoma with few inclusion bodies were selected as controls.

Summary

By electron-microscopic examinations, a phenomenon supposed to be the virus of trachoma was demonstrated from typical trachoma cases showing numerous inclusion bodies. No similar appearance was obtained from any of the non-trachomatous control cases.

The publication of this paper has been made possible through the kindness of Sir Stewart Duke-Elder.

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Brit. J. Ophthal. (1952) **36**, 586.

APPLIANCE

PORTABLE REFRACTION OUTFIT*

BY

J. W. BISHOP

Coventry

REFRACTION work, except under conditions to which one has become adapted, is always a somewhat frustrating occupation, and this I have found particularly so when doing domiciliary refraction work. However, much of the annoyance of this type of work may be avoided by a portable refraction outfit, made to my design.†

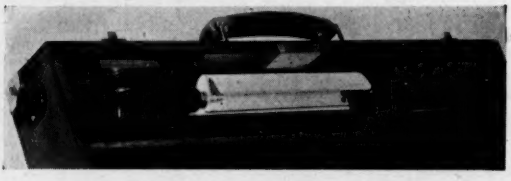

FIG. 1.—Electric bulb and battery to provide illumination.

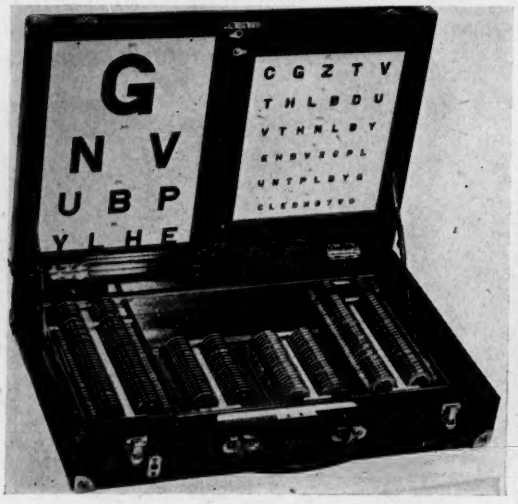

FIG. 2.—Test types and lenses.

The important features of this outfit are these:

(*i*) It is readily portable, its total weight being 21 lb.

(*ii*) It can be quickly set up in the patient's home or in a peripheral clinic.

(*iii*) The illumination for the test types is built into the lid of the case (Fig. 1). Though it does not altogether conform with ap-

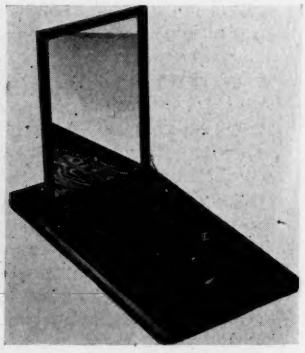

FIG. 3.—Mirror for reverse testing.

* Received for publication April 22, 1952.

† By Messrs. Rayner and Keeler, Ltd.

proved standards for the illumination of test types, I have found it adequate for domiciliary work.

(*iv*) The test types, also housed in the lid (Fig. 2), can be removed and turned round, one side being printed for direct vision, and the other for mirror testing. They are washable and the surface is non-reflecting.

(*v*) The mirror (Fig. 3) is readily adjustable and can easily be fixed at the desired angle if the size of the room necessitates reverse testing.

(*vi*) The mirror is incorporated in what is virtually a pad of Dunlopillo which holds the lenses in place during transportation of the outfit. This Dunlopillo allows one to stand the mirror on any surface without risk of damage.

(*vii*) The tray of lenses (Fig. 2) is removable, and can, of course, be used independently from the rest of the outfit.

(*viii*) The built-in spot-light to be used for muscle balance testing gives sufficient illumination in a dark room for retinoscopy.

CORRESPONDENCE

PTERYGIUM

To the Editorial Committee of the BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS—Mr. C. Heath states in the July number of your Journal (*British Journal of Ophthalmology*, **36**, 393, 1952) that several books on ophthalmic surgery have appeared since Kamel described his method of dealing with pterygium (*British Journal of Ophthalmology*, **9**, 549, 1946), but that as far as he is aware in none is Kamel's procedure mentioned.

If Mr. Heath will look in "Eye Surgery", 1st edition, 1946, p. 226, and 2nd edition, 1950, p. 320, he will find the full account which I wrote of Kamel's operation, and also accounts of other modern operations for this condition, such as D'Ombrain's.

Yours faithfully,

H. B. STALLARD.

81, HARLEY STREET,
LONDON, W.1.
July 17, 1952.

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BOOK REVIEWS

Le champ visuel—Topographie, normale et pathologique, de ses sensibilités. By A. DUBOIS-POULSEN. 1952. Published under the auspices of the Société française d'Ophtalmologie. Masson, Paris. Pp. 1175, 820 figs (4 plates).

The author, with his collaborators, has set out to provide a comprehensive study of all aspects of visual field examination, and a perusal of this volume leaves no doubt as to the success of the endeavour. For too long, Dubois-Poulsen believes, the investigation of visual field defects has meant nothing more than an outline of the peripheral limits and of localized central field changes, using a technique which varies from one examination to the next.

An histological introduction precedes the first part of the work, which provides a full exposition of the physiological principles and anatomical features underlying perimetric and campimetric studies. Included in this part of the book are chapters devoted to the definition of the limits of the visual fields, and to the importance of the qualitative and quantitative physical characters of the stimuli used in their experimental and clinical determination. The author's conception of threshold as a measure of sensitivity forms the basis of recording the topography of the field, and the isoptre is defined as the line joining points of the visual field having the same threshold. Having considered the known data on the topography of the field in conditions of illumination with white light, he makes a detailed study of the visual field during dark adaptation, of flicker perimetry, and of variations in colour sensitivity. The normal blind spot and angioscotomata have been carefully studied, and original work on the action of general factors and of a number of drugs on these scotomata is reported. A detailed description of the anatomical pathways for the visual impulses concludes the first part.

Passing from the precision of the physiological approach to the practical problems encountered in clinical examination, the second part begins with a description of the very many types of instrument used to record the visual fields, and their underlying principles. The clinical methods of perimetric and campimetric examination are, fortunately, fewer in number, and here again the material illustrates the author's determination to omit no relevant detail from the discussion.

After a short chapter on the general physiopathological characteristics of visual field defects follow nine chapters, occupying some 500 pages, devoted to a consideration of the field changes found in virtually any type of ocular pathology in which such changes are to be anticipated. The wealth of personal observations included in this major section of the book is most remarkable.

The appendix includes a simplified explanation of the physical principles of photometry, and those whose memory of this aspect of the subject is not recent might well study this short section before the main work.

The book achieves unity by constant reference to the notion of threshold as the basis for visual field investigations. An interesting observation concerns our uncertain knowledge of the threshold for colours, and in this matter the author concludes that there is little to justify the use of colours as a clinical method of examination.

No review of a book of these proportions, largely the work of a single individual—who generously acknowledges the help he has received from many of his colleagues—, can fail to take the form of an appreciation; there is no doubt that this volume will remain for many years a unique work of reference on the topography of the sensitivity of the visual fields.

Clinical Pathology of the Eye. By BERNARD SAMUELS and ADALBERT FUCHS. 1952. Cassell, London. Pp. 420, 418 illus., 191 col. (7 *guineas*).

This is a volume of considerable size designed not only to cover the whole of ocular pathology but also to correlate the histological appearances seen in diseased conditions

with the most prominent clinical features. It is not a systematized critical survey of the subject with bibliographical references, but an amplification of the lectures given by the two associated authors to their students, the one in New York and the other in Vienna; since they were both trained in the school of Ernst Fuchs, the Viennese influence on their pathological outlook is everywhere apparent. After a short introduction sketching the essential general pathological changes seen in inflammations, circulatory and metabolic disturbances, degenerations, and injuries, the various tissues of the eyeball are treated seriatim; the remaining chapters deal with myopia, tuberculosis, leprosy, and syphilis, post-operative findings, injuries, and tumours; the orbit and its contents are not included.

A feature of the book is the abundance of illustrations, and considerable reliance is placed upon them to amplify the text. With one exception they are drawings or paintings, and these are claimed to be more informative than histological photographs because they may be made to emphasize the important features of a particular preparation. The wisdom of this view. may be questioned, since, if a book of this kind is used as it ought to be, and read not in the study but in the laboratory or museum where the student has his own preparations to hand for comparison, the reader will find that the pictures, simplified and dramatized by the artist, give a biased and sometimes misleading representation of reality. The book, however, is pleasant to read; it presents a great deal of information in a simple and accessible manner, and is a considerable addition to ophthalmic literature.

NOTES

ILLUMINATING ENGINEERING SOCIETY

THE programme of meetings of the Illuminating Engineering Society in London and the provinces, which has just been issued for the new session beginning on October 1, 1952, includes over 160 events.

The second Trotter-Patterson Memorial Lecture is to be given on January 28, 1953, by Dr. E. D. Adrian, O.M., President of the Royal Society, who will speak on "The Nervous Reactions of the Retina".

Dr. W. J. Wellwood Ferguson, M.B., Ch.B., will give the Presidential Address on October 14, 1952 at the Royal Institution, Albemarle St., W.1, at 6 p.m.

DEPARTMENT OF OPHTHALMOLOGY

UNIVERSITY OF GLASGOW

DURING October, 1952, a series of meetings will be held in the Department on Wednesdays at 8 p.m. A discussion will follow the main paper.

October 8	-	Dr. F. W. Campbell, "Twilight Myopia".
October 15	-	Film, "Embryology of the Eye".
October 22	-	Dr. R. J. McWilliams, "Congenital Diseases of the Eye".
October 29	-	Dr. A. A. Douglas, "Prognosis and Orthoptics".

NORMAN McALISTER GREGG PRIZE

THE first award of the Norman McAlister Gregg prize will probably be made in 1955 or 1956. A bronze medallion depicting Gregg in bas-relief will be awarded, and it is expected that funds will permit the allocation of approximately £100 to each triennial winner. The Ophthalmological Society of New South Wales is trustee of the Gregg award, and the first impression of the medallion was presented to Norman McAlister Gregg last December at a complimentary dinner, held in the clubhouse of the Royal Sydney Golf Club, Rose Bay, which was attended by 133 of his colleagues, representing Sydney University as well as numerous medical institutions.

It will be recalled that in July, 1951, the University of Toronto honoured Gregg with the Charles Mickle Fellowship, awarded every decade to " that member of the medical profession who is considered to have done most during the preceding ten years to advance sound knowledge of a practical kind in medical art or science ". Since then Gregg has been awarded the Fellowship of the Royal College of Obstetricians and Gynaecologists, but his friends all over the world are well aware that no award or distinction, however exclusive, could possibly upset Norman Gregg's modesty. If ever a man deserved the title of Happy Warrior or Admirable Crichton, surely he does. Having gained two scholarships at Sydney Grammar School, he proceeded to win another at Sydney University, from which seat of learning he graduated with first-class honours. At the age of 14 he played in the 1st cricket XI of his school. He represented his University and the State of New South Wales in cricket and tennis. At Sydney University he even gained a half-blue for baseball. He was probably a good enough tennis player to represent Australia in the Davis Cup, but the first world war interfered with such activities. Here again Norman Gregg was in the forefront; he served for several years as a regimental medical officer in France, where he was wounded and gassed, and won the Military Cross.

The outcome of Gregg's clinical investigation into maternal rubella, which he began in 1940, is now familiar to every student of medical literature, and has indeed become known to innumerable laymen, but the younger generation is apt to forget how important a landmark was set up by the discoveries of this great clinician. Now that such a mass of evidence has been arrayed against rubella, it is easy to recognize that other noxious intra-uterine influences may well be responsible for congenital abnormalities formerly assumed to be the consequence of gene-defects. Gregg's conception opened up a vast field not only for speculation but also for practical research.

Amidst all these activities Norman Gregg has found time to be an inspiring university teacher, to conduct a busy practice, and to make fruitful contact with his colleagues in other continents. No man is more ready than he to help and encourage the young, and so we may confidently foretell that his example will stir competitors to produce work worthy of the Prize.

RULES OF THE NORMAN MCALISTER GREGG PRIZE

The following rules, adopted by the Council of the Ophthalmological Society of *New South Wales pursuant to the resolution of the society dated November 21, 1951,* take effect from February 7, 1952.

(1) The prize fund, to be known as the Norman McAlister Gregg Prize Fund, shall be administered by trustees being members of the society, who shall be appointed by the Council which shall have power to remove and replace the trustees from time to time at its discretion.

(2) The monies and investments from time to time comprising the prize fund shall be held by the trustees and paid or applied by them in such manner as the Council may direct.

(3) A competition for the prize, to be known as the Norman McAlister Gregg Prize, shall be held by the Council once in every three years, or at such intervals as the Council may determine.

(4) The value of the prize shall be such as the Council may determine from time to time, and the cost thereof and the expenses of administration of the prize shall be borne by the prize fund.

(5) Upon the cessation of the scheme for any reason whatsoever, the then unexpended balance of the prize fund shall be applied in such manner as the Council may direct.

(6) The conditions regarding the conduct of the competition and the award of the prize shall be such as may be prescribed by the Council from time to time, and in particular as follows:

(*a*) Subject to these rules the prize shall be awarded to the candidate whose work is deemed to be the most valuable contribution to knowledge in ophthalmology. On each occasion of the holding of the competition the Council may invite works on the above matter generally or on a specific subject or subjects.

(*b*) A candiate must be, and declare that he is, a British subject.

(*c*) The work submitted by a candidate must be in the English language. It must be his own and written since the prize was last awarded. If such work has previously been submitted for publication, details must be supplied by the candidate.

(*d*) The Council shall appoint examiners for each competition and the Council's decision as to the winning entry shall be final and conclusive.

(*e*) In the event of the Council being of opinion that no work is of sufficient merit, it shall not award the prize. The value of any such prize or prizes not awarded from time to time may be expended by the Council either in the purchase of books for the library of the society, such books to be subscribed "Donated by the Norman McAlister Gregg Prize Fund", or in such other manner as the Council may determine.

(7) Subject to any resolution of the society to the contrary, the Council may revise these rules from time to time and rescind, amend, or extend the same as it may deem necessary or desirable.

MR. JOHN MARSHALL, F.R.F.P.S.Glas., has been appointed Surgeon-Oculist in Scotland to Her Majesty the Queen.

MR. FRANK A. JULER, C.V.O., F.R.C.S., has been appointed Extra Surgeon-Oculist to the Royal Household.

MEDWAY AND GRAVESEND HOSPITAL MANAGEMENT COMMITTEE

St. Bartholomew's Hospital, Rochester

QUALIFIED ORTHOPTIST.—Required for post vacant now. Salary scale £370 x £12 10*s* to £420 *per annum*. Apply to Hospital Secretary giving age, qualifications, and details of experience, with copies of recent testimonials.

OBITUARY

CEDRIC KEITH COHEN

It is with great regret that we record the death of a well known Australian ophthalmologist. Dr. Cohen died suddenly of a coronary occlusion at his home at Sydney on July 26, 1952, in his 63rd year. He was the eldest son of the late John Cohen, a judge of the District Court of New South Wales and, at one time, speaker of the New South Wales Legislative Assembly.

Born at Brisbane, he was educated at Sydney Grammar School, and subsequently entered into residence at St. Andrew's College within the University of Sydney, graduating M.B. in 1914 and Ch.M. in 1915. After a period as house-surgeon at the Royal Prince Alfred Hospital he enlisted in the R.A.M.C. when a call came from Britain for medical graduates, and served for four years in France. After the armistice he remained in London and was appointed house surgeon at the Royal Westminster Ophthalmic Hospital, Chandos Street. He later returned to Sydney where he built up a successful practice as an ophthalmic surgeon, and was appointed to the staffs of the Sydney and Lewisham Hospitals.

Dr. Cohen relinquished his appointment to Lewisham after some 17 years but continued his association with Sydney Hospital, where he became senior ophthalmic surgeon, and finally consulting ophthalmic surgeon on his retirement from the active staff in 1950. During this 30 years of devoted service he conducted a big ophthalmic clinic and was most energetic in the interests of the hospital and its patients, his drive and initiative being largely responsible for the improvements made to the ophthalmic department.

He was associated with the examination and post-graduate teaching of students in ophthalmology at the University of Sydney, and on the foundation of the Royal Australasian College of Surgeons was elected a fellow. He was president of the Ophthalmological Society of New South Wales in 1932, and he became a foundation member of the Ophthalmological Society of Australia (B.M.A.). For 23 years he was a member of Legacy, an organization which gives medical, educational, and material aid to the dependants of deceased ex-servicemen, and became chairman of the medical committee.

Dr. Cohen was extremely fond of music and a most entertaining pianist. In any gathering his distinctive and genial personality attracted interest, and the warmth of his nature and his ready humour quickly established friendships. Dr. and Mrs. Cohen will be remembered by many of those who attended the International Congress of Ophthalmology in London in 1950 and by many European ophthalmologists whom they visited about that time. The outstanding impressions which this kindly ophthalmologist leaves with a host of grateful patients and sorrowing friends are those of a character of great benevolence and of a mind active and interested in all things.

Dr. Cohen's first wife died in 1929. He is survived by his widow, and by the daughter (Mrs. Donald Silver of London and Cyprus) and the son, Brian, of his first marriage. To these members of his family we extend our deepest sympathy.